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Diseases of the Nervous System

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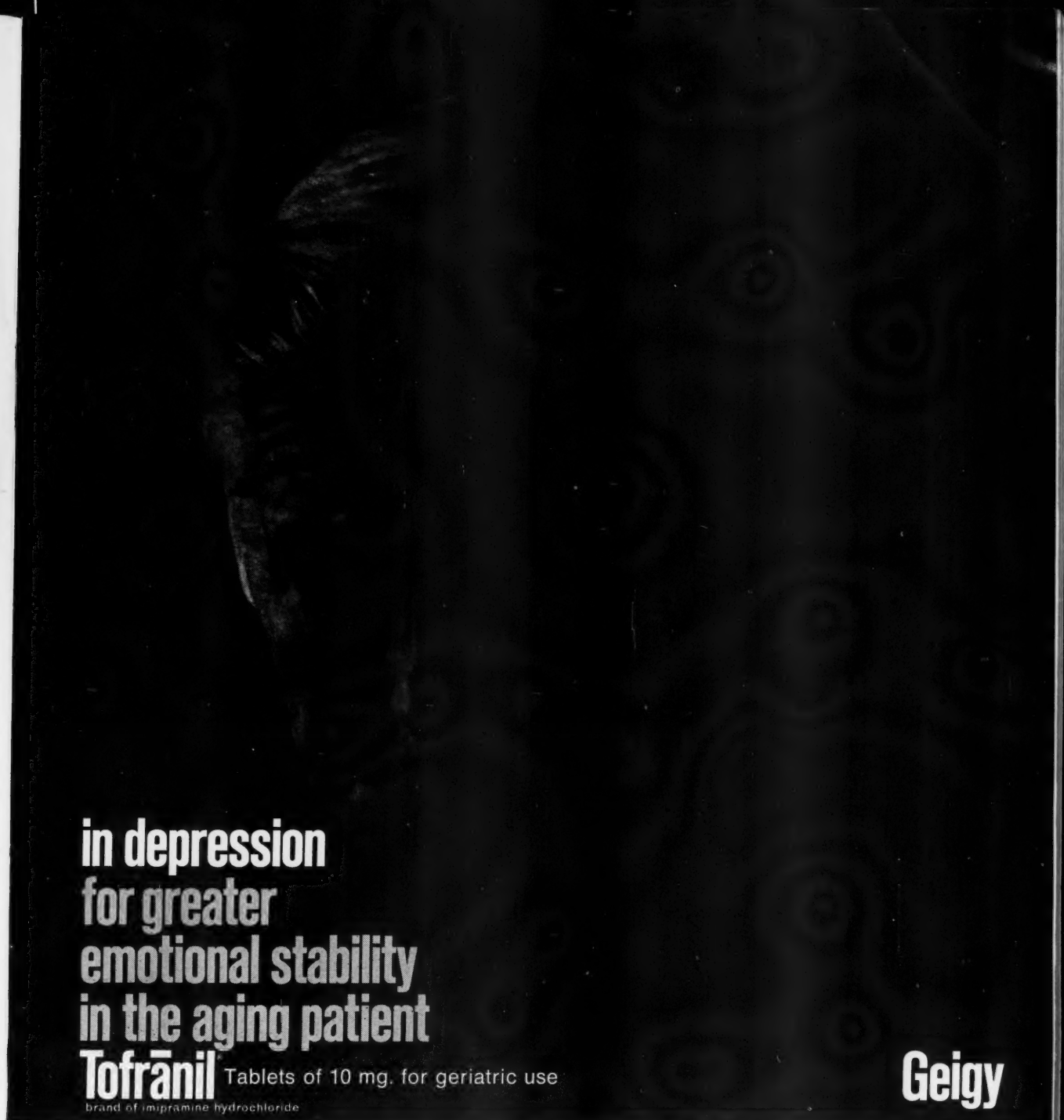

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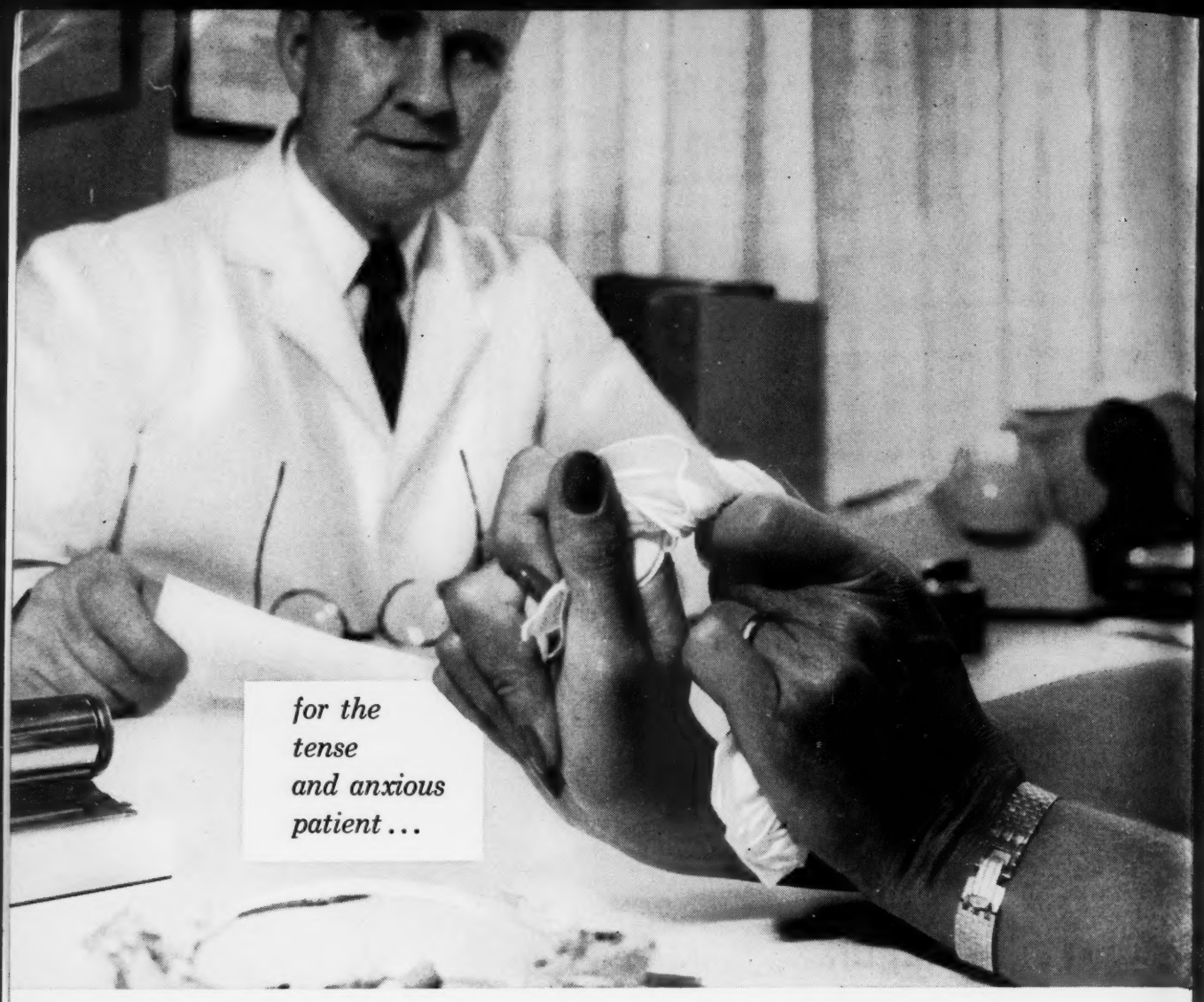

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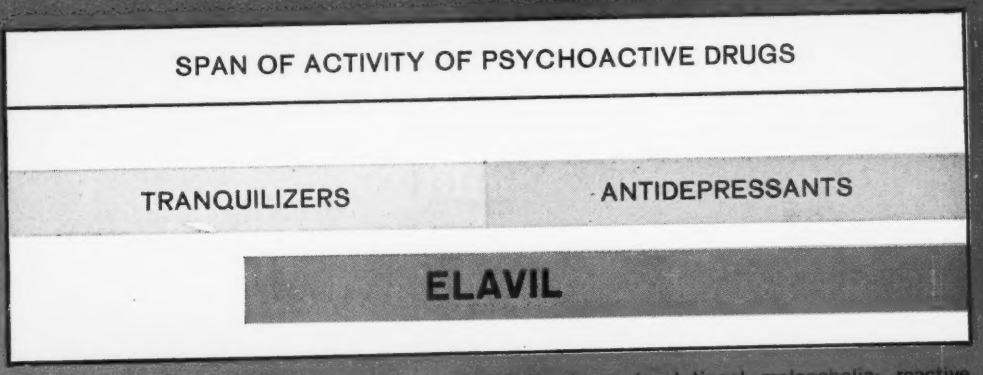

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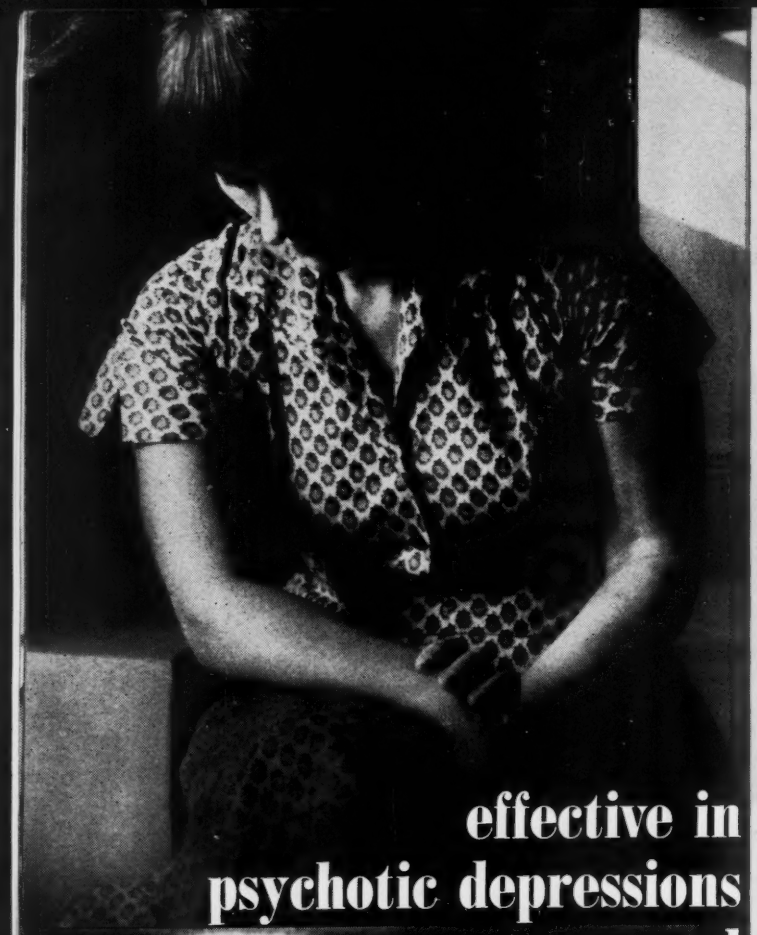

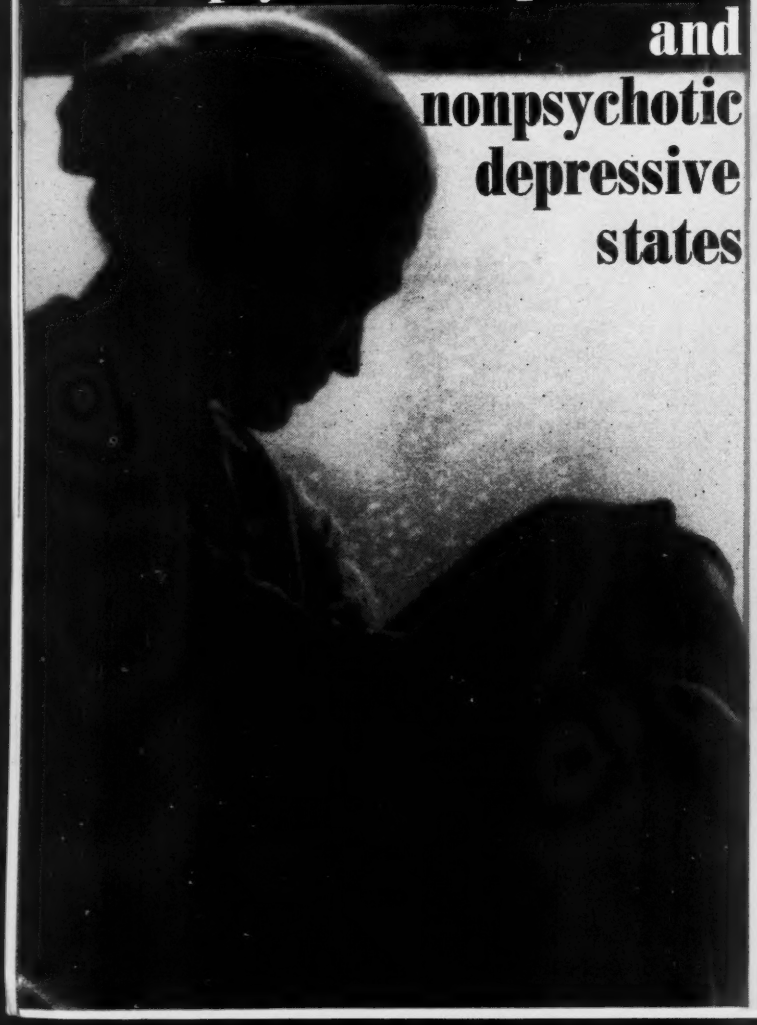

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

The Amyotrophic Lateral Sclerosis Syndrome

(An Exercise in Differential Diagnosis)

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DESMOND S. O'DOHERTY, M.D.

There are many diseases combining lesions of upper and lower motor neuron units which may be mistaken, at varying times in their course, for amyotrophic lateral sclerosis. Similarities in the ages of onset and the classical combination of upper and lower motor neuron signs may make the differential diagnosis difficult or even impossible in the early stages.

Considering the fact that the prognosis for amyotrophic lateral sclerosis is so poor and that in the other conditions, treatment, at least to some degree, is possible, one should be careful to rule out these other conditions before presenting the depressing prognosis of amyotrophic lateral sclerosis to the patient and his family.

Although amyotrophic lateral sclerosis is a disease of middle age, it may begin in age groups other than the 30-50 year range. Men are affected about twice as frequently as women.[1] While the disease attacks mainly the motor cells of the cortex and the anterior horns of the spinal cord, the motor cells of the basal ganglia are at times involved[2] giving rise to a parkinson-like picture.

Classically, amyotrophic lateral sclerosis begins in the cervical cord, usually as an anterior horn cell disease, producing lower motor neuron manifestations such as atrophy, weakness and fasciculations starting in the small muscles of the hand. Sometimes preceding, but usually following the onset of the lower motor neuron involvement, there is evidence of upper motor disease with exaggerated reflexes and the presence of pathological reflexes. Sensory changes, when present, are not on the basis of the degenerative disease itself and should lead to further investigation.[3] Involvement of motor neurons may occur in the brain stem giving rise to a picture of progressive bulbar palsy.

The prognosis is poor, the life expectancy being approximately three years in the case of the amyotrophic lateral sclerosis of the cord, and approximately eighteen months whenever the brain stem is involved.

Among the diseases more likely to be confused with amyotrophic lateral sclerosis are: cervical rib syndrome, syphilitic meningomyelitis, bilateral ulnar palsy, syringomyelia, several mid-line cervical cord compression diseases, such as mid-line cervical disc, and tumors of the cervical region, thyroid myopathy, and under rare circumstances, carcinoma of the lung.

We have also seen a patient with atrophy and fasciculations in lower extremities resulting from vascular insufficiency of the cord from marked atheromatous changes in abdominal aorta.

The Cervical Rib Syndrome

Only rarely is the cervical rib syndrome important in such a differential diagnosis; however, bilaterally occurring supernumerary ribs may give a moderately symmetrical picture of a lower motor neuron disease involving the hands.

Illustrative Case 1: A 22-year-old woman had a history of pain in the right hand with numbness along the thenar side for two months, and for several days prior to examination noticed a severe pain in the left arm and shoulder. There was also a questionable weakness of the left arm. Physical examination revealed moderate atrophy and fasci-

From Department of Neurology, Georgetown University Medical Center, Washington, D.C.

culations over the left supraspinatus and infraspinatus and triceps muscles, mild weakness in flexion and extension of the left arm and absent triceps reflex on the left. There were no objective sensory changes. X-rays revealed bilateral cervical ribs (Fig. 1).

Comment: It is rare to find a supernumerary rib syndrome without pain. The presence of severe pain, the scattered distribution of atrophy, sensory changes when present and the classical x-ray changes make the diagnosis relatively easy. It will be seen then, that this condition usually presents no hardship in differential diagnosis when thought of.

Syphilitic Meningomyelitis

Even before the introduction of penicillin in the treatment of syphilis, the parenchymatous types of lues simulating amyotrophic lateral sclerosis were relatively uncommon. This obviously will become less of a problem, since central nervous system lues is becoming almost a rare disease in the United States. However, there are still occasional patients admitted to busy neurological services who fall into this category.

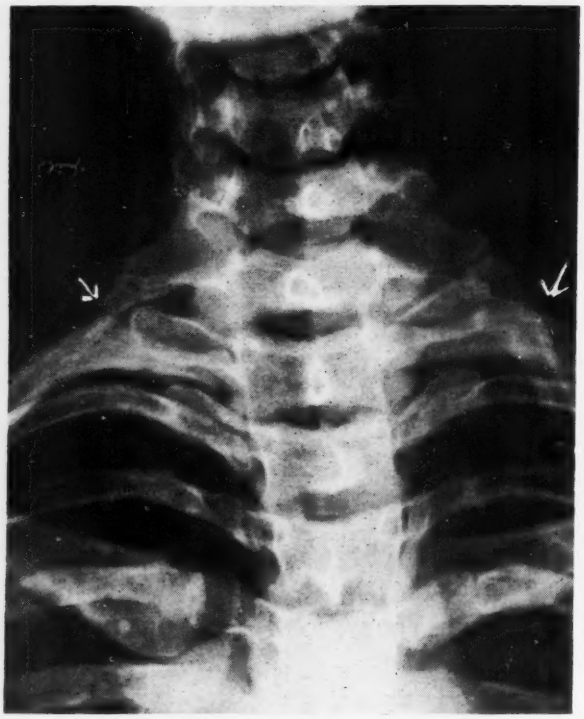

Fig. 1. Demonstrates bilateral cervical ribs, rudimentary on right, large on left. (Case 1.)

Illustrative Case 2: A 49-year-old colored male was admitted because of some disturbance of gait. He was unable to give a good history as to the onset, duration or progression of his symptoms. He had no subjective sensory complaints. On neurological examination the cranial nerves were found to be uninvolved. He walked with a wide-based gait and a decrease in associated arm swing on the right. There was mild hypertonus of the right upper extremity. Atrophy of the interrosseii and thenar musculature was present bilaterally. There was also atrophy over the biceps and deltoids, more noticeable on the left side. Weakness was present in abduction and adduction of the arms, flexion and extension of the forearms, and digital movements. Fasciculations were present over both pectoral groups, thenar eminence and the deltoid muscle on the left.

X-rays of the cervical spine, including special views of the odontoid process were normal. The spinal fluid showed an increase of protein (282 mg.%), a 4+ Kahn test. There were no cells present.

Under treatment with penicillin the patient showed noticeable improvement and was discharged on the twenty-ninth hospital day.

Comment: This case could very well have been diagnosed as amyotrophic lateral sclerosis on the first examination; however, the spinal fluid serology suggested a treatable condition in which treatment with penicillin was associated with improvement. Usually the spinal cord type of parenchymatous lues is associated with a slower course and some sensory change; however, in some cases lateral columns may be affected alone (Erb's spastic paraplegia). The slower course, presence of sensory changes and typical spinal fluid changes are enough to diagnose this condition.

Bilateral Ulnar Neuropathy

Atrophy of the small muscles of the hand, secondary to changes in the ulnar nerve, sometimes occurs secondary to pressure at the elbow, leprosy or diabetes but occasionally without any demonstrable metabolic or mechanical pathology.

Illustrative Case 3: A 63-year-old retired policeman was admitted to the hospital because of a right-sided Jacksonian motor seizure and aphasia. This aphasia lasted for about 24 hours and gradually cleared up. However, at the time of examination it was noted that there was atrophy of the dorsal interosseii bilaterally (Fig. 2), which the patient stated had been slowly progressive over a

Fig. 2. Demonstrates atrophy of first dorsal interossei muscles in a patient with bilateral ulnar neuropathy. (Case 2.)

period of years, first noted when he was a motorcycle policeman. It had been relatively static in the past four or five years following his retirement. He had no evidence of any fasciculations; there was a hypalgesic pattern in the right ulnar distribution. It was considered that this was on the basis of peripheral neuropathy secondary to vibration trauma.

Comment: We are acquainted with a second patient who developed atrophy of the interosseii muscles from the handling of a vibratory tool used to trim hedges. Following the discontinuation of its use, the patient made a gradual recovery.

In these cases the exact distribution in the ulnar and/or median nerve musculature, and the presence of sensory change, either objectively or subjectively, are the important keynotes in making the differential diagnosis.

Amyotrophic lateral sclerosis resulting from the use of vibratory pneumatic tools has been reported.[4] While no long tracts were involved there was a description of fasciculation in the upper extremities suggestive of anterior horn cell involvement. Our cases, though, are definitely peripheral nerve disease and not a result of vascular cord changes.

Syringomyelia

Rarely should syringomyelia be confused with amyotrophic lateral sclerosis since it ordinarily begins at an earlier age, and is characterized by sensory changes in the "shawl" distribution; that is, over the shoulders and extensor surface of the forearm. Occasionally, however, the syrinx may begin in the anterior part of the cervical cord, present itself as a disease of the anterior horn cells and only later in its course extend to the lateral columns. Sometimes sensory changes may be absent or mild, or purely subjective so that no sensory pattern is obtained by examination.

Illustrative Case 4: A 54-year-old colored female had a history of slowly progressive stiffness of the left hand involving the fingers; there was no pain. Weakness appeared and became slowly progressive. About three years prior to admission she began to notice some wasting and drooping of the left shoulder. Gradually there was a complaint of stiffness in both legs. Two years prior to admission she complained of some burning of the left arm and shoulder. There were no paresthesias or dysesthesia. There was no tingling or numbness. She was admitted to the hospital for workup. At that time the cranial nerves were within normal limits except for a mild ptosis on the right side, associated with a slight difference in pupillary size, the right being smaller than the left. There were no gross differences in sweating. There was mild limitation of neck motion; no pain was elicited. The main neurological deficit was in the motor system. There was atrophy bilaterally involving the hands, the right more affected than the left; (Fig. 3) atrophy of the biceps and triceps bilaterally, again the right more than the left, and atrophy of the deltoid, trapezius and supraspinatus muscles bilaterally. All reflexes were decreased in the upper extremity, and all reflexes were increased in the lower extremity. There was bilateral ankle clonus and Babinski signs were present. There was a vague mild hypalgesia over the right arm. This was not a clear cut sensory pattern.

Fig. 3. Demonstrates atrophy of dorsal interossei in patient with syringomyelia.

Lumbar puncture was normal in pressure, dynamics and showed normal protein. VDRL and colloidal gold were normal and there was an absence of cells.

A myelogram was done which was normal. A starch iodine test (Fig. 4) showed a definite Horner's syndrome on the right side.

Comment: Usually the syringomyelia begins earlier in life and the history is longer than in amyotrophic lateral sclerosis although cases such as the illustrative one above, starting later in life, occur. There are almost always sensory changes present. These, together with the Horner's syndrome, are enough to rule out amyotrophic lateral sclerosis. When ptosis is mild and questionable, a starch iodine test is a simple way of verifying the presence of the Horner's syndrome.

Cord Compression

Several cervical cord diseases may produce direct pressure on the anterior part of the cervical cord. Specifically, these are protrusion of the cervical disc in the midline and extramedullary cord tumors. Figure 5 shows in some detail the mechanism by which the cord is involved both from compression and also from interference with the blood supply from the anterior spinal artery, thereby giving rise to a deficit which may extend above and below the level of the pressure.

Fig. 4. Starch-Iodine test showing right Horner's syndrome in patient with syringomyelia (Case 3), showing a right ptosis and absence of sweating.

Mid-Line Cervical Discs

Such lesions are much more frequent than have been previously supposed. While lateral protrusions are more common than those in the mid-line, mid-line discs are more insidious in their course and certainly have a more serious implication. Whiplash injuries of the neck are frequently the cause and may precede the onset of symptoms by as long as ten years. Usually, however, no history can be elicited. Pain, while a common symptom with the lateral protrusion, is not prominent in the mid-line discs. The signs and symptoms are those of anterior horn cell and lateral column disease. The motor signs are far more prominent than the sensory.[5,6]

Surgical treatment frequently being helpful, at least for arresting the disease, it is imperative that a diagnosis be made early before permanent cord changes have taken place.

Illustrative Case 5: A 59-year-old colored male was admitted because of weakness in the right arm starting three years before, first noted starting in the fingers of the right hand and associated with some twitching of the muscles of the hand and forearm. The picture was slowly progressive for two years; at that time there was weakness of legs, definite wasting of the muscles of the hands and later in forearms and shoulders on the right side, and to a lesser degree, on the left, with fasciculations noticed in all these areas.

At the time of admission to the hospital the cranial nerves were all within normal limits. The motor system showed atrophy of the right biceps, triceps, deltoids, pectoralis and intrinsic muscles of the hand. There were no fasciculations of the tongue, but fasciculations were seen over the right arm and forearm. There was weakness of both arms more on the right, and spasticity and weakness of both legs. Hoffman's sign was present on the right. All reflexes were hyperactive; there was no clonus at the knee or ankle. Babinski and Gordon signs were present on the right side. At the time of his admission the referring clinic felt that this was a case of amyotrophic lateral sclerosis. On examination the patient showed the findings described above with a questionable C5, C6 dermatome sensory loss.

X-rays of the cervical regions showed narrowing and calcification suggestive of old herniated discs at C5-C6 and C-6 and C6-C7. A myelogram was done which showed multiple abnormalities at these

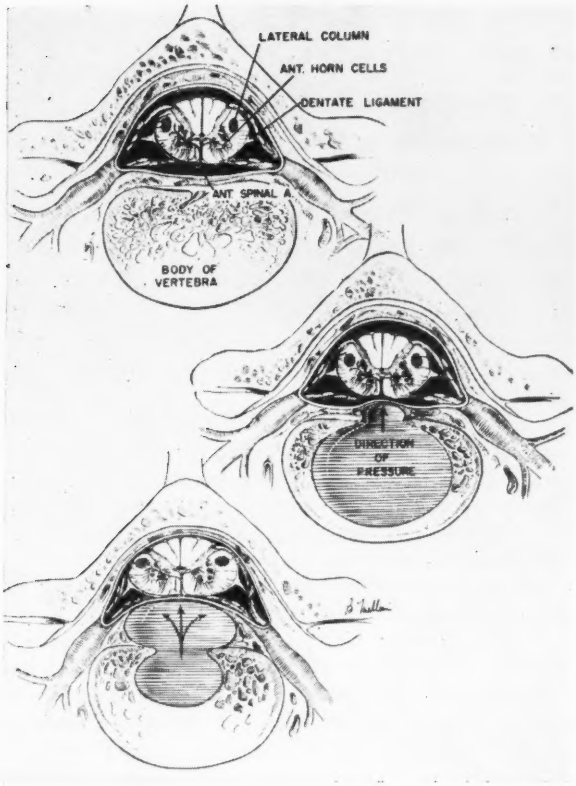

Fig. 5. Three diagrams showing changes taking place from midline pressure diseases such as cervical disc, dislocation or tumor; as the pressure increases there is interference with the anterior spinal artery and direct pressure in the anterior horns and indirect pressure on the lateral columns because of tightening of the dentate ligament.

levels (Fig. 6). As a result of this a laminectomy was done in the cervical region from C4 to C7. The spinal cord was exposed. There was chronic arachnoiditis and calcified herniated discs, the dentate ligament was dissected on both sides. The spinal cord was pale in color.

This patient has shown a gradual but marked improvement over the past year. Much of the muscle bulk has returned and he continues on physical medicine with what could be estimated at a 60 to 70% recovery to the present time.

Comment: A clear-cut C5, C6 segment sensory deficit would have made this picture much clearer. However, this was difficult to elicit and the main feature on which to suspect the diagnosis without laboratory help was that of the slow prolonged course.

Here it is necessary to point out that the laminectomy does more than remove the discs; indeed, many of the discs are so calcified as to be impossible to move and are therefore left in. Cutting the dentate ligament relieves the pressure on the cord and allows the cord more mobility. Freeing of the adhesions is frequently helpful in restoring cord circulation.

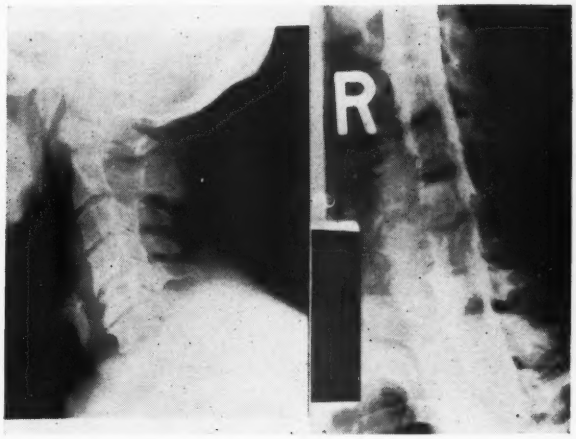

Fig. 6. Demonstrates narrowing of C4-5, C5-6, C6-7, and myelogram indicating multiple herniated discs. (Case 4.)

Cervical Cord Tumors

Extramedullary cord tumors are approximately three times more common than the intramedullary type and are more likely to be confused with amyotrophic lateral sclerosis. Among the commonest are meningiomas, neurofibromas, sarcoma and metastatic carcinoma. Through the mechanism described above (Fig. 5) these tumors may produce a syndrome of upper and lower neurone involvement on a mechanical basis.

Illustrative Case 6: A 38-year-old white female was admitted for evaluation because of mild pain in the left shoulder, aggravated by motion and occasional numbness radiating into the right hand. She had had a diagnosis of carcinoma of the breast eight years before which was treated with a right mastectomy; five years later a lymph node biopsy from the right axilla showing questionable metastasis was made. At the time of this admission a neurological examination showed that the cranial nerves were not involved, the right arm was larger than the left. There was atrophy of both hypothenar eminences, and weakness of the movements of the hand and fingers. There were no sensory changes.

Spinal fluid examination was normal in all aspects; x-rays showed changes suggestive of metastasis in the sixth and seventh cervical vertebra and there were other evidences of bony metastasis to the thoracic cage suggestive of mestastatic disease (Fig. 7). The diagnosis was established as metastatic adenocarcinoma.

Fig. 7. Showing bony erosion resulting from metastatic carcinoma. (Case 5.)

Comment: There are usually enough indications of central nervous system involvement in metastatic disease to enable one to make this diagnosis. However, there are cases in which a long interval separates the original diagnosis and the central nervous system metastasis. Less frequently the central nervous system may be the first system to signal invasion by metastatic neoplasm. In these cases a high index of suspicion would prompt one to search carefully through the x-rays for other evidences of metastasis.

Increase in spinal fluid protein or changes in colloidal gold reaction or a block in the Queckenstedt maneuver, are also helpful. In the above patient, such maneuvers were not useful. In the case of the primary extramedullary tumors, surgical removal is often attended with satisfactory results and for this reason such investigation is warranted. The presence of pain is a common finding in these tumors. Sensory changes of the root type may also be found; these plus the change in spinal fluid dynamics and protein, and erosion of vertebrae are enough to make a myelogram necessary.

Chronic Thyrotoxic Myopathy

This condition is not likely to be important numerically. A small number of patients with thyroid disease will show a muscle wasting syndrome usually beginning after forty-years of age, involving the proximal musculature mostly, but occasionally the small muscles of the hands; there are usually other manifestations of thyroid disease.

Illustrative Case 7: A 44-year-old colored male was admitted because of chronic thyrotoxic symptoms over a four year period, with weight loss, edema, cardiac decompensation, fatigue, tremor and heat intolerance.

On physical examination he displayed signs of thyrotoxicosis, including tachycardia (P. 120) exophthalmos, warm skin, goiter, with bruit over the thyroid, and mild cardiac decompensation.

There was wasting of the shoulder and pelvic musculature and also atrophy of the small muscles of the hands (Fig. 8).

The protein bound iodine (PBI) and radioactive iodine uptake (RAI) were both elevated.

On antithyroid therapy he improved in his thyrotoxic signs, gradually gained weight and showed improvement in his atrophy over the next eight months.

Comment: The signs of thyrotoxicosis are usually, but not always obvious, and at times may be overlooked. Abnormalities in laboratory studies such as serum cholesterol, PBI, and RAI are invariably present and are enough to make the diagnosis when a myopathic syndrome accompanies these abnor-

Fig. 8. Atrophy of hands in two patients with thyrotoxic myopathy.

malities. The myopathy is not associated with fasciculations.

Treatment of the thyroid condition, as in the case of the above patient will bring about improvement of the myopathic picture as well.

Carcinoma of the Lung

Non-metastatic syndromes with central and peripheral nervous system involvement may occur in carcinoma, particularly of the lung. Such lesions may be on the basis of a neurotoxic effect or be on a deficiency basis due to a metabolic defect. Rarely, the picture is that of a spinal cord syndrome simulating combined system disease or amyotrophic lateral sclerosis.

Illustrative Case 8: A 54-year-old white male was admitted with a three-month history of weakness and weight loss, gradually progressing to loss of ability to walk. He had been a heavy smoker, and had a chronic cough. X-ray of the chest, six months prior to admission had been normal. Physical examination at the time of admission revealed a combination of upper and lower motor neurone disease with atrophy, generalized, but more marked distally, there was bilateral hyperreflexia with pathologic reflexes. Chest films now showed possible lung tumor, verified by bronchoscopy. He rapidly deteriorated and died on the thirty-first hospital day. There was no evidence of metastasis, but the cord showed definite lateral column and anterior horn cell disease (Fig. 9).

Comment: It is quite possible that with the increasing attention paid to the neurological syndrome associated with carcinomas, not only of the lung but elsewhere, more amyotrophic lateral sclerosis syndromes will be found to be on this basis. There will possibly be some sensory changes if some degree of peripheral neuritis is present.

The diagnosis of a possible operable lesion may be delayed if carcinoma is not considered in the differential diagnosis of amyotrophic lateral sclerosis, particularly where lower motor neurone disease without fasciculations is present.

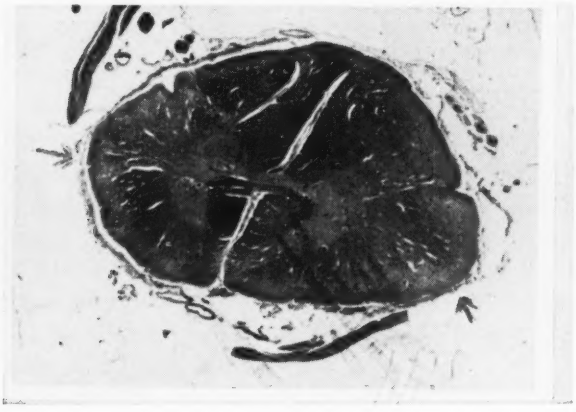

Fig. 9. (Luxol fast blue PAS.) Section of cord showing demyelination of lateral column (arrow). Anterior horns were severely involved. (Case 7.)

Discussion

It is evident then, that a group of diseases other than amyotrophic lateral sclerosis may produce a combination of upper and lower motor neurone involvement. Some of these are uncommon, as syringomyelia, bilateral ulnar atrophy, and those cases secondary to tumors; however, the classical amyotrophic lateral sclerosis is uncommon also, and may not occur as frequently as midline cervical disc.

One should be careful to do whatever tests are necessary to establish the presence of these other treatable conditions. The main feature of differentiation should be the presence of fasciculations in a widely distributed area, as in the arms and legs. This, in the absence of central nervous system syphilis, may be enough to definitely establish the diagnosis. In the absence of these, however, every patient with weakness and atrophy of the small muscles of the hand should have x-rays of the cervical spine and possibly a myelogram. This assures early diagnosis and the onset of treatment before permanent changes take place.

Chart I gives a summary of the points helpful in making the differential diagnosis.

Summary

1. A group of conditions is presented which may at times be confused with amyotrophic lateral sclerosis.

2. In view of the lack of treatment in amyotrophic lateral sclerosis and the possibility of surgical or medical treatment in these conditions, it is important to consider these diseases in the differential diagnosis of amyotrophic lateral sclerosis.

CHART I

Comparison of Amyotrophic Lateral Sclerosis with Various Conditions

Disease	Usual Age at Onset	Changes in Sensory Shpere	Atrophy	Fasciculations	Spinal Fluid	X-Rays	Myelogram
Amyotrophic Lateral Sclerosis	Middle age 30-50	None	Distal	Marged; start distally in hands — Generalized	Negative	Negative	Done when no fasciculations in lower extremities
Cervical rib	Early adult under 30	Frequent pain and numbness	Usually mild Distal	Rare	Negative	Characteristic Fig. 1	Not indicated
Syphilitic Smeningomyelitis	Middle age	Patchy or absent	Common Diffuse	Common; Mild and diffuse	Abnormal protein, serology Colloidal gold	Negative	May be indicated negative
Ulnar atrophy	Over 30	Ulnar distribution; may be subjective	Small muscles of hand	None	Negative—usually increased protein with diabetes	Elbow may show callous formation	May be indicated negative
Syringomyelia	Under 30—usually	"Shawl" distribution	Small muscles of hand	Frequent Distal	Negative unless block present	May show congenital anomalies	Indicated intramedullary lesion if cord swollen
Midline cervical disc & spondylosis	Middle age	Usually absent in disc. May be in neck or shoulder	Patchy, Distal	Common but mild	Negative unless block present	Characteristic narrowing or subluxation Fig. 6	Indicated Shows disc or block
Tumors	Any age	Pain frequent, may be no sensory loss	Common; may be mild	Uncommon	May show block or increased protein	Bony erosion	Indicated characteristic defect or block
Chronic thyroid myopathy	Middle age	None	Marked—usually proximal	May be present but not common	Usually normal	Negative	Not indicated

3. The mechanism by which space taking lesions of the cervical cord produce upper and lower motor neurone signs is shown.

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Comments on Huntington's Chorea

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Huntington's chorea has been known for many years. In its fully developed form, the clinical picture is well crystallized. The combination of heredofamilial background, adult evolution, choreiform movements and progressive mental deterioration constitutes a readily identifiable condition. Nevertheless, it is surprising how often the disease may pass unrecognized for a considerable period. Some of the descriptive and diagnostic terms used by physicians illustrate this lack of recognition. Such phrases as the following have appeared on the admission certificates of patients with frank Huntington's chorea: "senile dementia," "menopausal dementia," "marked toxic delirium," "depressed and negativistic," "athetoid movements," "petit mal," "Parkinson's disease," "uncoordinated movements—disease of the cerebellum," "peculiar twitchings of the neck," "presenile dementia—possibly Alzheimer's," and "cerebral degeneration following Parkinson's disease" It appears, therefore, that this disease, even in comparatively full bloom, may not be recognized. Diagnostic difficulties are further increased in the period preceding development of well defined choreiform movements. The eugenic importance of prompt diagnosis is, of course, indisputable. Accordingly, we have reviewed a series of cases of Huntington's chorea, most of which have been under our direct observation, with the purpose of crystallizing factors which may be diagnostically helpful, especially in the early stages.

This study is based on a series of 57 cases which have been observed at this institution since 1933. As may be inferred the disease is not common. It has been estimated[1,2] that the frequency of Huntington's chorea is approximately 5 or 6 per 100,000 of the general population. This would imply an overall incidence of some 9,000 to 11,000 cases in this country. Of the 57 cases 32 (56%) were female and 25 (44%), male. This represents a slight reversal of the usually accepted mild preponderance in men; it corresponds to similar findings in an earlier study by Falstein and Stone.[3] The 57 patients stemmed from 35 separate families.

With respect first to heredofamilial background, it may be stated that in 48 subjects the family record was positive with respect to the occurrence of Huntington's chorea. In the remaining nine patients, all of whom presented a classical clinical picture of the disease, the family history was ostensibly negative. Similar gaps in the heredofamilial background have been reported by others.[3] Of these nine patients, one individual was an adopted child whose true lineage was unknown; in three instances no family history was obtainable; in three cases the other members of the family had remained in Europe and their medical records were unknown; in one instance the patient's father had died at a relatively early age; and in one case incidence of Huntington's chorea in the family was denied by the informant. It might be indicated further that 7 of the 9 patients, in whom positive family history was lacking, are now deceased. Postmortem examination was permitted in 5 of these 7 individuals. All revealed pathological changes in the brain indicative of Huntington's chorea.

Thus, in evaluating the family history, appropriate allowance must be made for such factors as inadequate or unobtainable records; geographical separation of families with resultant defects of history; adoption, with subsequent ignorance of true lineage; death of a parent prior to the appropriate age limit; and, on occasion, either ignorance, or reluctance of the family to submit information concerning this aspect of the family history. The last factor, which has also been emphasized by other investigators, is demonstrated in this brief case report.

E.T., a 49-year-old male, was admitted in 1958 from a local veterans' hospital. The observations and conclusions of the staff at that institution were summarized in the committing physician's statement: "History of present illness-onset of illness approximately two years ago with facial tics. On-

From Fairfield State Hosp., Newtown, Conn.

set of disturbance of gait one year ago. In past six months has had deterioration of memory and general intellectual functioning. For past two months is withdrawn, apprehensive about health.

Physical findings—negative except for ? cerebellar signs on neurological, hyperactive D.T.R's. Pneumoencephalogram suggestive of atrophy.

Mental condition — apprehensive, preoccupied, moves with jerky, explosive movements, manneristic, dysarthria. Impairment recent memory. Preoccupied with health and especially 'diarrhea.' No hallucinations, but somatic delusions possible.

Presenile dementia, possibly Alzheimer's."

The description, as recorded, is characteristic of Huntington's chorea. Yet the appropriate diagnosis was not made, presumably chiefly because pertinent family history was not made available. Following his transfer to this hospital, the subject was promptly identified as the son of a patient who had had Huntington's chorea and had expired at this institution seven years previously. Personal knowledge of the family background and continuity of medical attendance thus confirmed the clinically recognizable condition.

Finally, it should be emphasized that an apparently negative family history at an earlier temporal period may later become positive by the appearance of the disease in a previously asymptomatic sibling. Thus the diagnosis may be ultimately established in a bizarre or previously doubtful case, as illustrated in Winn's report[4] and in the case of A.F., reported below.

With respect to racial distribution, it is well established that the disease may occur in all races. Accordingly, this factor is of no diagnostic importance. In the present series, 36 subjects were of at least second generation American stock and, as might be expected, most of these families came from Connecticut or nearby New York. The remainder were distributed racially as follows: Irish 5, German 1, Swedish 2, Lithuanian 2, Austrian 3, Jewish 2, Italian 1, Colored 3 (all members of the same family) and unknown 2. Wilson's[5] impression that the disease is more frequent among southern European peoples is not confirmed in this series.

The age of onset of the disease has been well defined. All reports are in agreement that the peak incidence occurs in the latter portion of the fourth decade and the early years of the fifth decade of life. A few comments concerning the extremes of the age period may be pertinent. It is also agreed that the disease may appear, without undue rarity, before the age of 20 and after 60. Davenport indicated that about a sixth of his large series of cases commenced by the age of 20. This figure is higher than that indicated in other reports. Bell[6] reported that approximately 10% of 460 cases began before the end of the second decade; Falstein and Stone[7] found 2 of 55 cases (4%); and Huet's[8] figure was 4 of 67 individuals (6%). Hughes'[9] series of 143 patients included 4 (3%) whose onset was before 20 and 13 (9%) if the 20th birthday were included in the temporal period. In the present series satisfactory information concerning the age of onset was available in 52 cases. Of these, 3 (6%) began before the age of 20. The youngest was 16. At the other end of the age axis, Hughes reported that 3 of 143 cases (2%) began after the age of 60; Huet's data included 2 of 67 (3%); and Falstein and Stone found 11 of 53 cases (21%). In the present series there were 5 individuals (10%) whose illness was apparently first manifested between the ages of 60 to 70. The oldest was 70. In brief, therefore, it is apparent that despite the accepted peak incidence of the disease, Huntington's chorea may be initiated at almost any period of life prior to the senium. Onset after the age of 70 is rare and in such instances chorea due to senile or vascular changes should be suspected.

With respect to the type of onset, it has been indicated repeatedly that emotional and behavioristic abnormalities frequently precede the onset of frank choreiform movements. Yet this sequence of development does not seem to be generally appreciated. This observation is quite disparate from the conclusion[9,10] that emotional or personality abnormalities do not possess predictive value with respect to the ultimate development of the disease in members of choreic families. A number of individual reports as well as psychiatric and neurological textbooks have affirmed that Huntington's chorea is frequently ushered in by personality changes,

emotional abnormalities, gradual withdrawal, disinterest and other psychic alterations. Precise evaluation of the sequence of events has not been so well defined.

The present study revealed the following information concerning this area of interest. In 19 cases (33%) emotional and personality alterations were emphasized as the earliest symptoms; in 13 instances (23%) choreiform movements appeared first; in 14 cases (25%) the two components began more or less concurrently; and in 11 cases (19%) the exact temporal relationship could not be established. Of course, these figures must be regarded as only approximate. Admittedly, it is difficult to crystallize the onset of an insidious disease such as Huntington's chorea. The delineation of both time and type of onset will depend to some extent on the alertness, sophistication or general orientation of the observer, on the one hand, and the clarity of evolution of objective features, on the other. Thus, to some observers, truculence, assaultiveness, temper tantrums, and destruction of clothing and furniture might constitute more incisive historical landmarks than the appearance of a few minor twitchings awkwardness of gait, or general clumsiness. Conversely, rapid development of choreic movements and dysarthria might constitute a clearer crystallization of the onset of the disease than gradual withdrawal, asocial tendencies, or disinterest. Despite these qualifications, it is apparent that in a very significant proportion of cases the onset of Huntington's chorea is characterized by the appearance of psychic, rather than neurologic changes. These psychic alterations may precede the development of choreiform movements by months or even years. Obviously in this phase diagnostic difficulties are maximal.

The most frequently encountered psychic symptoms are recorded in the following table. This includes all cases in the series, irrespective of whether the psychic symptoms preceded, followed, or were concurrent with the development of the neurological components. Analysis of the data from this standpoint did not reveal any significant differences.

TABLE I

Early Psychic Alterations Observed

Symptom	No. Cases
1. Temper tantrums and outbursts, threatening attitudes, abusiveness, combativeness, assaultiveness and physical violence, throwing or destroying things	36
2. Irritability, obstinacy, argumentativeness, querulousness, quarrelsomeness	23
3. Emotional instability, impulsiveness, excitability, crying episodes, moodiness, childishness, "hysteria," nervousness	22
4. Depression, suicidal ideas or threats, frank suicidal attempts, depression and anxiety about inheritance of disease	21
5. Untidiness, decline of interests, neglect of personal appearance and household, withdrawal, seclusiveness, self-preoccupation, inattentiveness, indolence	28
6. Jealousy, suspiciousness, accusations, ideas of infidelity, paranoid ideas or delusions	12
7. Other—restlessness, setting fires, fear of being alone, excessive drinking, sexual preoccupation, somatic complaints, self-exposure, grandiosity, insomnia, hypercriticality, obscenity, frank psychosis	30

It is apparent that some type of emotional alteration occurred most frequently. Differentiation among the first several items in the table is difficult. However, the first group is intended to denote various degrees of emotional abnormality which were associated with the implication of accompanying physical disturbance; the second is devoted to changes revolving about irritable, obstinate attitudes; and the third to more diffuse phases of emotional lability. The fourth group is confined to more specific depressive features. Another major set of symptoms included general withdrawal, asocial trends, untidiness and constriction of interest. These features may of course, be early indications of the later, progressive mental deterioration. Another set of symptoms, which occurred with some degree of frequency, included paranoid, suspicious attitudes, particularly ideas of infidelity directed against the spouse. The final group of symptoms included non-related features, each of which occurred in two or more cases. Some are reflections of disturbed judgment, reduction of normal ethical or moral control, or other disturbance of higher cerebral functions.

The relative frequency of suicidal attempts, either abortive or consummated, by individuals with Huntington's chorea has

been reported repeatedly. In this series of cases, the histories indicated that five individuals voiced suicidal threats and six made frank suicidal attempts. Our experience indicates, however, that suicidal features occur essentially in the early phases of the disease, as they were not observed in any patient following hospitalization. Presumably this is related to the increasing mental deterioration and apathy.

The occurrence of frank psychoses, either affective or schizophreniform in nature, years before the appearance of frankly recognizable chorea, has been reported frequently. Three patients in this series underwent hospitalization for a preliminary psychotic episode. In another instance the onset of the disease was characterized by the appearance of a catatonic-like episode. Two of these cases appear to be of particular interest:

E.T. was first hospitalized in November 1943 at the age of 43. Shortly prior to his commitment he had been apprehended by police for molesting a woman on the street. While incarcerated in jail, he exhibited various behavioristic abnormalities; for example, he paraded about in the nude, he assumed pontifical attitudes. He voiced a number of delusions; that he had a special mission on this earth—to protect married men from loose women.

At the time of his first admission, no pertinent family history was obtained—possibly due in part to limitations of personnel during the war period. In the early course of hospitalization he exhibited numerous behavioristic difficulties. He attempted to hide in various areas and to approach female patients. On the occasion of visits by his family he would make open sexual advances toward his wife, and he attempted to rape his adolescent daughter. A diagnosis of dementia praecox, paranoid type was made. After a degree of improvement he was released in October 1944.

He was readmitted in March 1951. The interval history indicated that during the preceding four years he had attended the neurological clinic of a local general hospital. This record revealed that "he had developed athetoid movements and had become progressively more belligerent and paranoid." He was hospitalized at another local hospital in December 1950 after a second suicidal attempt in which he had jumped from a second story window and had sustained a fracture of the first lumbar vertebra and a Pott's fracture of the right ankle. He was described as being uncooperative and incontinent. Choreiform movements were noted.

At the time of his readmission a family history, heavily tainted with Huntington's chorea, was obtained. The patient was withdrawn, irritable and paranoid in his attitude. Neurological examination revealed choreiform movements, dysarthric speech and hyperactive reflexes in the lower extremities. He expired in January 1952 at the age of 51. Postmortem examination revealed changes characteristic of Huntington's chorea. It might be added that this patient's daughter was hospitalized six years later, at age 28, with Huntington's chorea.

A.F. was first hospitalized in May 1950 at the age of 47. At that time the family history revealed that her mother was living and relatively well at 82; her father had died at about 42 years of age, when the patient was six. The anamnesis revealed some loss of interest and diminution of activities for almost a year. For several months prior to hospitalization she was unduly concerned about her health. She complained vaguely of somatic difficulties, referable chiefly to the gastrointestinal tract. She exhibited "nervous episodes" and tantrums in which she would scream at her husband. She failed to accomplish her usual household tasks and her husband had to assume many of these duties. She would sit idly, fussing about her abdominal complaints or picking at her skin. Psychiatric examination revealed a whining, complaining individual who exhibited a stereotyped preoccupation with her health. She was somewhat retarded. Occasionally, she would voice incongruous, inappropriate remarks. Neurological examination revealed the presence of brisk reflexes and a transient clonus and equivocal Babinski on the right. On psychological tests she achieved a full scale I.Q. of 80; the record was suggestive of organic impairment. The diagnosis was not well crystallized; however, it was finally recorded as involutional melancholia. She made a satisfactory adjustment in the hospital and was released in August 1950.

She was readmitted five years later. The interval history revealed that she had adjusted fairly well until a year prior to rehospitalization. She then became increasingly more careless about her personal appearance and household chores. She appeared withdrawn, secretive, and uncooperative. She was argumentative with her husband and neighbors. At night she insisted on leaving lights burning in the bedroom so that finally it was necessary for her husband to remove the light bulbs every evening before retiring. In the physical sphere, progressive weakness and imbalance had appeared. Neurological examination now revealed characteristic choreiform movements, hyperactive reflexes, bilaterally positive Babinski and unsustained ankle clonus. In the interim between this patient's hospitalizations, her sister had been admitted to this hospital with obvious Huntington's chorea. Thus the diagnosis was clearly established and confirmed. It might be indicated further that the patient's mother finally expired at this hospital at the age of 87 of senility; presumably, the heredi-

tary trait had been transmitted by the father who had remained asymptomatic up to his death at 42.

In the case of E.T. there were no clues pointing to the final correct diagnosis at the time of the patient's first hospitalization. Even if the family history had been available, it would have been difficult to equate that episode of mental illness with the onset of Huntington's chorea. Contrariwise, the case of A.F. is one in which the earlier addition of a positive family history would have created strong suspicion of the correct diagnosis. The combination of ill defined psychic abnormalities, alteration of reflexes, and tentative indications of organic impairment on psychological tests, in the presence of a positive heredofamilial background, should direct the physician's attention to the diagnosis of Huntington's chorea, even in the absence of choreiform movements.

Later psychic changes are, of course, characterized by progressive mental deterioration with features similar to those resulting from any organic cerebral impairment. These changes occur most consistently, although Minski and Guttmann[11] described one family in which mental deterioration was lacking. In the absence of progressive mental deterioration, some other type of chorea should probably be suspected.

With respect to neurological findings, emphasis has been devoted almost entirely to the extrapyramidal features. Relatively little attention has been devoted to the state of the reflexes. Most standard neurological texts lack any reference to this phase of the neurological status in Huntington's chorea. In Wilson's authoritative text it is affirmed: "Apart from mental and extrapyramidal symptoms the nervous system is, as a rule, functionally intact." Merritt[12] stated: "Sensation remains intact and the reflexes are normal." However, Jelliffe and White[13] indicated that, "the knee jerks are active or uninvolved," and in a more recent text Alpers[14] asserted: "The tendon reflexes are at first normal but later become overactive." Similarly, most psychiatric texts fail to make reference to this specific item, although Noyes,[15] and Henderson and Gillespie[16] noted that "the tendon reflexes are increased." Thus there has been relatively scant attention to, or information concerning this portion of the neurological status.

For some time we have been impressed by the frequent occurrence of hyperactive reflexes in this disease, and this impression has been confirmed by the data of this study. Table II summarizes the state of the reflexes and associated pyramidal tract signs, as revealed by a single examination, in this series of patients with Huntington's chorea.

TABLE II

Hyperactive Reflexes and Associated Signs

Sign	No. Cases
Hyperactive reflexes	21
plus transient or unsustained ankle clonus	7
plus positive Babinski	2
plus positive Babinski and Hoffmann	3
plus positive Hoffmann	2
plus positive Babinski, Hoffmann and ankle clonus	1
plus positive knee and ankle clonus	1
plus equivocal Babinski	2
Total	39

Thus 39 of the 57 cases (69%) revealed hyperactive reflexes (particularly the quadriceps) and in 18 instances this finding was accompanied by some other evidence of pyramidal tract involvement. Multiple examinations through the years might well have increased this incidence. Efforts to delineate any specific temporal relationship of this finding to the duration of the disease were not successful. It might be indicated that most of the patients were hospitalized after the disease was relatively well advanced. However, it is interesting to note the findings in several specific cases. Two patients (a pair of twins), in whom the diagnosis was made very early, before the development of frank choreiform movements, did not exhibit hyperactive reflexes. On the other hand, in the case of A.F., noted above, hyperactive reflexes and transient ankle clonus were present at the time of her first admission to the hospital, several years prior to the crystallization of the disease.

Pleydell[17] has stressed the importance of dyslalia as an early sign and has affirmed that Huntington's chorea should always be considered whenever difficulty or hesitancy of speech occurs in early adult life. The data obtained in this group of patients did not

appear to lend definite confirmation to this conclusion. Dysarthria was emphasized by the informant in eight cases. In only one instance could it be regarded as an early feature; in the other seven cases choreiform movements had already been established so that the speech difficulty could not be regarded as an early manifestation. Dysarthria as an integral feature of the fully developed disease is encountered regularly.

Brief comment concerning the choreiform movements themselves may be pertinent, chiefly with respect to their status in the early and late stages of the disease, when the chorea may not be manifested in characteristic form. It is well to remember that at first there may be merely some awkwardness of gait, clumsiness, dropping of objects, minor twitchings of face or shoulders, lack of quietude, fidgetiness and excessive, ill-harmonized movements. At times the patient may make some effort to disguise the excessive purposeless movement with an apparent afterthought of purposeful direction. As the disease advances, typical choreiform movements become fully matured. With the passage of years, however, the intensity of the chorea may subside, and again the patient manifests chiefly an awkward, ungainly gait, dysarthria, minor twitchings and movements, and lack of repose. Huntington's chorea may also occur. In this series sine chorea one patient presented this particular type of involvement. The diagnosis was supported by the presence of mild ungainliness, dysarthria, profound intellectual deterioration and a heavily tainted family history.

The electroencephalogram offers some supportive diagnostic assistance. Early studies indicated that the EEG is abnormal in a high proportion of cases of Huntington's chorea; however, the pattern is not a specific one. Electroencephalographic examinations could be performed in only a few of our cases. They revealed usually mildly abnormal records in diffuse, non-specific fashion. It is interesting to indicate that the records of two patients (the pair of twins noted above) showed some degree of abnormality at a very early phase of the illness, and prior to the appearance of choreiform movements. In this regard it is pertinent to note the work of Patterson et al.[18] who found the EEG of predictive value in the children of choreic families. However, this conclusion has not been confirmed.

Discussion

We have been concerned chiefly with the features which may be helpful in the early diagnosis of Huntington's chorea, prior to the development of a fully crystallized clinical entity. It is apparent that the heredofamilial background is an important consideration which will direct attention to the correct diagnosis in many instances. However, there may be gaps in the family history due to a variety of causes. These gaps will be reduced by the physician's personal knowledge of the family record; however, death of one or both of the parents prior to the appropriate age limit may be an additional obstacle. An apparently negative family history may, in turn, be rendered positive by the appearance of the disease in a previously asymptomatic sibling. In instances of well defined disease, which includes all other aspects of the condition, the diagnosis can be made appropriately, even if the available family history is presumably negative. It is doubtful, however, whether such cases represent instances of the disease arising *de novo*. In our experience, it is more likely that there is merely a deficiency of knowledge or that information has been deliberately or unwittingly withheld or altered. It is not rare, for example, for an informant to indicate that a member of the family died of a "brain tumor," or "hardening of the arteries" or some other condition, only to discover, by communicating with the appropriate hospital, that the disease was actually Huntington's chorea. Despite the well recognized peak of onset of the disease, it is well to remember that Huntington's chorea may be initiated at practically any age period, from adolescence to the senium. Thus the age factor, within the limits indicated, should not be a barrier to consideration of the appropriate diagnosis.

It should be emphasized that more frequently than not the disease is initiated by psychic alterations rather than neurological

changes. In the main these consist of emotional changes in which features such as irritability, obstinacy, temper tantrums, assaultiveness, emotional instability and depressive components loom large. General withdrawal, apathy, loss of interest and inattentiveness are also encountered frequently. They may be the forerunners of the later, progressive mental and intellectual deterioration. Jealous, suspicious, paranoid type of reaction is not rare, and finally there may be a wide variety of other behavioristic abnormalities or antisocial acts, reflecting defects of judgment and ethical sense, which may bring the individual into the public eye. The type of psychic alteration does not seem to depend upon whether these abnormalities precede, follow, or intervene concurrently with the choreiform movements.

Aside from the extrapyramidal features, neurological changes—specifically, hyperactive reflexes, particularly of the quadriceps—are frequent. There may also be additional, associated signs in the form of unsustained or transient ankle clonus and positive Babinski and Hoffmann. It is difficult to indicate how early in the course of the disease these features may appear but there is suggestive evidence pointing to the assumption that, in some instances at least, they may be present long before choreiform movements are manifested. Dysarthria is common; it is not, as a rule, an early manifestation but occurs in combination with other classical neurological features. The EEG may reveal diffuse, non-specific abnormalities in many instances. Psychological tests frequently give evidence of organic deterioration.

It may be concluded, therefore, that in an individual with a family history of Huntington's chorea, the development of personality alterations and evidences of impairment of emotional control should direct the physician's awareness to the possibility that this status represents the onset of Huntington's chorea. The additional finding of hyperactive reflexes, with or without associated pyramidal tract signs, lends further probability to the presence of the disease. Further tentative confirmatory signs are abnormalities in the electroencephalogram and evidences of organic deterioration in psychological tests.

Summary

A study of 57 cases of Huntington's chorea revealed that the onset of the disease is associated with the development of personality and emotional alterations. In many instances these psychic changes precede the development of choreiform movements. Hyperactive reflexes, with or without associated pyramidal tract signs, are frequently present. In the presence of a positive family history, the appropriate diagnosis should be suspected in any instance in which these features appear, even though choreiform movements are not yet manifested.

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Marplan in the Treatment of Depression

(A Preliminary Study)

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From a neuropsychiatric viewpoint interest in the amine oxidase inhibitors began after the observation of mood elevation as a side effect of the hydrazines in the treatment of tuberculosis. The side effect led to the discovery that iproniazid, which is a hydrazine, was an amine oxidase inhibitor. The enzyme, amine oxidase, had been discovered many years earlier.

Among the amines oxidized by this enzyme are serotonin, epinephrine and norepinephrine. Serotonin is found chiefly in platelets, the chromatin cells of the intestinal tract and the brain. The quantity of serotonin in the brain parallels closely that of norepinephrine.[1]

It was discovered that the administration of reserpine caused a fall in the levels of serotonin, along with a behavioral change.[2,3] It is postulated that reserpine releases serotonin from a bound to a free state and thus is more readily oxidized by amine oxidase.[3,4] When an amine oxidase inhibitor was given prior to the administration of reserpine neither the fall in serotonin levels nor the pattern of depression took place.[5] Thus, the stage was set for a full investigation of amine oxidase inhibitors and their usefulness in neuropsychiatry.

One of the newer amine oxidase inhibitors is Marplan (1-benzyl-2-[5-methyl-3-isoxazolylcarbonyl] hydrazine), introduced for the metabolic treatment of certain neuropsychiatric disorders. The potency of Marplan in potentiating serotonin both *in vitro* and *in vivo* has been found to be many times that of iproniazid.

The purposes of this study were two-fold: First, to gain suggestive evidence of the clinical efficacy of the drug through a careful evaluation of the response of a group of patients who demonstrated depression as the outstanding clinical symptom; second, to evaluate its toxic potential by means of periodic, precise determinations of its effect on hepatic, renal, and hematopoietic tissues.

Material and Methods

The in-patient division of the Psychiatric Department of the Philadelphia General Hospital, Philadelphia, the setting for the study, is a unit of more than 200 beds with an admission rate of eight to ten patients per day. After discharge from the hospital, upon completion of the necessary in-patient treatment, a significant majority of patients are referred to the out-patient division of the Psychiatric Department of Philadelphia General Hospital for follow-up care. This particular organizational structure proved advantageous for those patients who responded to the total treatment situation with rapid and sometimes dramatic improvement. When these patients were discharged from an in-patient status to their homes, subsequent evaluations were carried out in the clinic.

Thirty consecutive adult patients were chosen for study from current admissions to the in-patient division of the Psychiatric Department between August 1959, and February 1960. The only criterion for selection was the presence of depression as the predominant clinical finding.

The possibility that some cases of depression passed through the psychiatric service without being detected because of faulty interviewing techniques must be acknowledged. Nevertheless, within the limits of our perceptiveness and alertness, every consecutive case of depression was included in the study, with only two known exceptions. Both of these individuals were diagnosed as manic-depressive reaction, depressed type, with a history of repeated depressive episodes, hospitalization, and rapid, successful remissions with ECT therapy. In their cases, it was decided that a prolonged period of hospital treatment, with a resultant absence

from employment and loss of income, would constitute a serious hardship. Accordingly, they were treated by the more conventional methods of ECT therapy, which had repeatedly proven so successful in their previous illnesses.

A Depression Rating Scale was drawn up to determine the presence and degree of depression (Table I). Both psychiatrists independently conducted psychiatric evaluations prior to the inception of treatment, and six subsequent evaluations at two-week intervals during the twelve-week period of treatment established as adequate, for purposes of the study. The presence of the different symptoms and signs was noted on the Depression Rating Scale at each examination; the degree of each symptom was indicated as severe, moderate, and mild.

The group consisted of 22 females and 8 males. The female patients ranged in age from 25 to 71 years, with an average of 52, and the male 32 to 62 with an average of 43 years. The average age for the entire study group was 50 years.

TABLE I

Depression Rating Scale

Research No. .....

Date .....

Ward .....

Name .....

Address .....

Age ..... Sex ..... Race ..... Marital Status .....

Examiner .....

Symptoms:

1. Despondency, sadness
2. Fatigue
3. Lack of interest and emotional response
4. Helplessness, hopelessness, pessimism, and despair
5. Feelings of incapacity and inferiority
6. Suicidal drive
7. Delusions of guilt and unworthiness
8. Hypochondria and psychosomatic complaints
9. Insomnia
10. Anorexia and weight loss
11. Self-depreciation

Signs:

1. Depressed appearance and attitude
2. Psychomotor retardation
3. Agitation

With the selection of patients based upon the presence of depression as a predominating feature of the clinical picture, it was inevitable that the patients would fall into different diagnostic categories. There was remarkably little disagreement about diagnosis between the two psychiatrists, with only one patient really presenting a classification problem and this a minor one, namely, differentiating between psychotic depressive reaction and manic-depressive reaction, depressed type. The diagnostic groups were distributed as follows:

	No.
Involutional psychotic reaction	13
Psychotic depressive reaction	5
Manic depressive reaction, depressed type	3
Neurotic depressive reaction	2
Schizophrenic reaction, paranoid type	3
Schizophrenic reaction, chronic undifferentiated type	3
Schizophrenic reaction, schizo-affective type	1
	30

An attempt to rate the patients according to the severity of depressive symptomatology found the psychiatrist investigators in remarkable accord: half showed a severe degree of depression, and half, a moderate degree.

Suicidal drive was present in 14 patients, with four of the patients having been admitted to the hospital as a direct result of a suicidal attempt. Two other patients gave a history of recent abortive suicidal actions. Altogether, six patients were rated as severely suicidal and eight moderately so.

Only eight had no history of previous psychiatric hospitalization, the remaining 22 patients totaling 45 previous admissions for in-patient psychiatric treatment. The oldest patient in the study was a 71-year-old woman with a diagnosis of manic-depressive reaction, depressed type, with a history of five previous hospitalizations for depression. Her previous hospital stays had varied in length, ranging between six and twelve weeks. In the past, she had responded well to ECT therapy. On the drug, improvement appeared at four weeks, and had progressed to an excellent degree by eight weeks. She was discharged at the end of ten weeks.

Initially, each of the patients received a

physical examination and psychiatric evaluation by the interne and resident on the particular service to which the patient was assigned in accordance with routine procedure of the department. They also underwent the routine testings and diagnostic procedures: hemoglobin, WBC with differential, fasting blood sugar, and urea nitrogen determinations; along with serology tests, electrocardiogram and 14 x 17 inch x-ray of the chest. After a patient was deemed suitable for the study from a psychiatric standpoint, a medical history was taken and a physical examination performed by the internist investigator. Final inclusion in the study was dependent on his clearance.

If there was a history or clinical evidence of hepatic or renal disease, or of a blood dyscrasia, or any finding that suggested the possibility of such pathology the patient was rejected for the study. Three patients were found medically unsuitable for the study by the internist investigator at his initial evaluation: one with chronic renal disease; one with a history of hepatitis, and an enlarged, irregular liver and one with an abnormal response to the liver function tests.

Before prescribing Marplan the following determinations were done on each patient: hemoglobin, KBC, urinalysis, SGO-T and BSP. These tests were repeated every two weeks for the duration of the patient's stay on the project. In addition, each patient received a physical check-up every two weeks or oftener as determined by complaints or appearance of objective signs.

The initial dosage in every case was 10 mg. t.i.d. In only five cases was the initial dosage level increased, 50 mg. daily in one, and 40 mg. daily in four patients. Only one of this group completed the study with improvement, rated as moderate in degree, the other four being grouped among the failures.

Results

The degree of the patient's improvement upon completion of twelve weeks on the drug was rated according to the Depression Rating Scale as excellent, good, moderate, slight, or failure.

Sixteen patients (53%) were rated as excellent recoveries. Of this group, seven patients were completely asymptomatic; nine patients retained only one or two symptoms to a mild degree.

Three patients (10%), completed the study with good results. On the Depression Rating Scale, one patient retained three symptoms to a mild degree; the second patient retained three symptoms to a mild degree, and one to a moderate degree; and the third patient retained five symptoms of depression to a mild degree.

Moderate improvement was seen in four patients (13.3%) at the end of 12 weeks. In this group, there was symptom retention ranging from seven symptoms of mild degree to three of moderate degree.

One patient (3.3%), showed slight improvement.

Finally, six patients (20%), failed to respond to the medication to any significant degree. All but one of the patients were dropped from the study prior to the expiration of the twelve-week investigation period. The duration of Marplan therapy varied from 3 to 10 weeks. This deviation from the original design was necessitated by the patients' complete failure to respond to the drug. More especially, the intensity of symptoms and the attendant suffering made a different therapeutic approach imperative.

Of the patients who responded favorably to the drug, 14 began to improve at the end of 2 weeks, 8 after 4 weeks, and only one showed a delayed response with symptom alleviation appearing only after the sixth week of treatment.

When a patient's response to treatment was marked by a rapid remission of symptoms, arrangements were made for discharge from the in-patient section prior to the termination of the twelve-week study period, with subsequent follow-up in the out-patient clinic, on a maintenance dose of Marplan adjusted to the clinical status of the patient. Thus, one patient was able to leave the hospital after only four weeks of treatment; 2 patients after 6 weeks, 3 patients after 8 weeks, and 5 patients after 10 weeks. Ten patients were discharged from the hospital at the end of the twelve-week study period. Two patients, both male schizophrenics, re-

mained within the hospital despite significant improvement of their depressive symptomatology, in order to receive further treatment for their basic psychiatric disorder.

Thus, 21 or all but two of the patients included in the excellent, good, and moderate improvement groups eventually were referred to the out-patient clinic for follow-up. Six patients failed to initiate clinic visits. The remaining 15 were followed for periods ranging from 3 to 8 months subsequent to the study. Two patients developed recurrences of their depressive illness. The rest all held their improvement, with several reporting progressive symptomatic relief.

Of the two patients who again became ill, one was a 61-year-old woman moderately depressed, whose illness was characterized by the most severe hypochondriasis and psychosomatic complaints of anyone in the study. This depressive illness was her third in sixteen months. Her improvement on Marplan was rapid, although a mild degree of somatic preoccupation persisted. She began attending clinic after 12 weeks of in-patient drug treatment. Marplan was discontinued one month after her discharge from the hospital. Three months later her symptoms recurred and she was rehospitalized.

The second patient was a woman of 58 years, who was undergoing her fifth depressive illness when admitted to the study. She had a long history of severe constipation and insomnia. Her depression was accompanied by marked agitation. She improved slowly on Marplan and at the time of her discharge from the hospital after 12 weeks of treatment, still complained of a moderate degree of insomnia and showed mild agitation. As an out-patient she continued to receive Marplan for 6 weeks. Her remission held for 10 months, when a recurrence of depressive symptomatology more severe than before developed, making it necessary to admit her again to the hospital.

Medical Aspects:

No abnormalities of hemoglobin, leukocytes, urine, or hepatic functions developed during the 12 weeks of investigation.

The safety of Marplan is further substantiated by the fact that it was well tolerated by a young male diabetic patient, without untoward effect on his metabolic disease, and a female patient on medical treatment for a duodenal ulcer. Her progressive improvement on a medical regimen was unaffected by the concomitant use of the antidepressant medication. Finally, two cardiac patients, one 18-months' post-myocardial infarction, another with a 5-year history of angina, reported subjective improvement of their medical symptoms.

Side Effects:

Two of the patients in this series complained of pruritus after receiving the drug for two weeks. One of them complained also of paresthesia. These symptoms disappeared in one week, and ten days respectively, although the drug was continued.

One patient developed a maculopapular rash with pruritus two weeks after being on Marplan therapy. Within seven days after the dosage was reduced from 30 mg. to 20 per day, rash and pruritus disappeared.

Ankle edema not attributable to cardiac, renal, hepatitic, vascular or electrolytic etiology, developed in two patients, but this condition vanished on conservative therapy —ace bandages, and elevation.

One patient had an episode of hypotension, fall in systolic blood pressure of 25 mm. of Hg., after being on medication for four weeks. This quickly returned to normal after she assumed the supine position, and the condition was avoided by the simple expedient of having the patient lie down for 20 minutes after ingestion of medication.

The patient who developed unilateral ankle edema also had several episodes of blurring of vision for a period of two weeks but this symptom gradually disappeared.

None of the side effects encountered required discontinuance of the medication and in the patient who developed a maculopapular rash the dosage was reduced.

Discussion

Undoubtedly, our results would have been more meaningful had a system of careful controls been built into the study. The contributions to the improvement of the patient of a sympathetic, therapeutically oriented

staff, including psychiatrists, nurses, attendants, recreational and occupational therapists were undoubtedly considerable. The removal of a patient from a disturbing environment to a setting where genuine concern and interest are consistently shown likewise, exerts its therapeutic effect. Finally, the tendency of depressed patients to enter into spontaneous remission must be considered in evaluating the results. However, despite the limitations of the study, the results offer strong presumptive evidence of the efficacy of Marplan in the treatment of depression.

Our second purpose was admirably served by the study. The results indicate that Marplan is a safe drug to administer. There was no evidence of liver toxicity based upon careful tests of function. The comparatively mild side effects appeared in only 20 per cent of the patients and at no time required discontinuance of the drug.

Some attempt was made to explain the differences between the recovery group and those patients classed as failures. Certain trends noted are presented in lieu of a clear delineation of the precise role of Marplan in the treatment of depression.

The seven patients rated as treatment failures (including the one patient rated as slightly improved), fell within four diagnostic groups as follows:

Involutional psychotic reaction	4
Psychotic depressive reaction	1
Manic depressive reaction, depressed type	1
Schizophrenic reaction, schizo-affective type	1

Thus, patients classed as involutional psychotic reactions, while making up 43 per cent of our patient population, accounted for 57 per cent of the failures. However, the significance of an analysis of results based upon diagnosis is vitiated by the difficulties of attempting to pigeon-hole depressed patients into the diagnostic categories established[6] in the Diagnostic and Statistical Manual of the American Psychiatric Association, especially with respect to involutional psychotic reaction, psychotic depressive reaction, and manic depressive reaction, depressed type. Rather extensive experience in the evaluation of depressed patients leads to the inevitable conclusion that there is significantly greater agreement between diagnosticians concerning the degree of depression than about the diagnosis itself.

The specificity of Marplan for the alleviation of depression is suggested by its effect upon those of our patients who were classified as schizophrenic. All but one of these seven showed a significant improvement in their depressive symptoms. The schizophrenic features, however, were unaffected, and required additional treatment including psychotherapy and tranquilizers to effect a remission and hospital discharge.

Contrary to the results of some other investigators,[7] who noted that neurotic depressive illness responded less satisfactorily to antidepressive medication than psychotic depressive illness the two cases diagnosed as neurotic depressive reaction responded promptly to Marplan. Although these individuals presented the clinical picture of a psychoneurotic disorder, they both gave a history of previous acute depressive illnesses, suggesting the possibility that the underlying emotional disturbance might have been psychotic in nature.

The same proportion of males and females failed to respond to the drug. However, the degree of improvement among the women was significantly greater, with 64 per cent showing excellent or good results, as compared with 50 per cent of the men.

The results indicated that the likelihood of recovery was greater if a patient was undergoing his first depressive illness requiring hospitalization. The eight patients in this category had either excellent or good recoveries except for an individual from "skid row" who showed strong paranoid elements and whose past history remained obscure because of his unreliability as an informant.

Among the patients who were not undergoing their first depressive illness, the ones who recovered and the failures showed essentially no difference in the number of previous hospitalizations.

The average age of the recovery and failure groups was remarkably similar, 50 years and 51 years respectively.

Severely depressed patients made up 70 per cent of the failure group. Among the patients who responded to the drug, 43 per cent were initially rated as severely depressed, with the remainder showing a moderate degree of depression. It would appear that the more severe the depression, the less chance of a favorable response to treatment. Although undoubtedly significant as a trend, there is the fact that the recovery group included ten severely depressed patients, several of whom responded dramatically.

An analysis was made of the symptoms that proved most refractory to treatment. Among the group of excellent recoveries, six patients retained a mild degree of insomnia and hypochondriasis. Two patients had complaints of mild fatigue and agitation.

The patients rated as having made good to moderate recoveries, complained of the following symptoms, in order of diminishing frequency and intensity: insomnia, hypochondriasis, agitation, fatigue, weight loss, and depression.

The emphasis on insomnia may be, in part, an artifact, since the nocturnal decibel level on the wards is frequently more conducive to the waking state than to slumber.

Summary

Thirty male and female in-patients who demonstrated depressive symptomatology, of severe to moderate degree, as the predominant characteristic of their psychiatric illnesses were administered the monoamine oxidase inhibitor, Marplan, over a period of 12 weeks. With only a few exceptions, the maximum dosage was 30 mg. a day. The patients were evaluated independently by two psychiatric investigators, initially, and at two-week intervals. Significant improvement ranging from excellent to moderate degree resulted in 77 per cent of the cases.

Extensive medical evaluation including periodic blood and urine studies and tests of liver function, the SGO-T and BSP, revealed no abnormalities developing from the medication. Six patients developed mild side effects including edema of the lower extremities, hypotension, pruritus, and paresthesia. These symptoms disappeared either spontaneously or with conservative treatment, without discontinuing the drug.

On the basis of this preliminary study, it is concluded that the results furnish presumptive evidence of the efficacy of Marplan in the amelioration of depression. Convincing evidence of the safety and low toxicity of Marplan was obtained.

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Newer Concepts of Feminine Personality

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It is only within the last hundred years that psychiatrists have attempted to look within and understand the development and structure of personality. Sigmund Freud, the father of psychoanalysis and a giant among thinkers, was one of the first to attempt to bring order out of chaos. There is general agreement about the remarkable perceptiveness and accuracy of his observations of human behavior. However, about the theories evolved from his observations there has been considerable diversity of opinion; and nowhere, it seems to me, is this more true than in regard to his theories about the psychology of women. Many of his theories had biological roots, and he developed his concept of bisexuality from the fact that there is a common embryological origin for the male and female organs rather than the fact that a child's significant experiences and psychic growth occur in relation to a mother and father, in our social situation. Thus, he viewed male and female as coexisting and inversely proportional to each other in a given person on a biological base, and without consideration of the dynamic interplay between parents and children.

Just as the Biblical Fathers in writing the Old Testament believed that God made Man in his image, so Freud viewed the male body as the prototype of humanity, and considered the female as defective or lacking. He believed that little girls considered themselves wounded or damaged, since they did not possess a penis, and he developed a compensatory concept for the female in which he viewed the maternal function, specifically, ability to produce a child—as compensation for the absence of a male organ. One cannot help but wonder why he did not assume that the child views his body image as natural, whatever its structure, until real handicap or environmental prejudice forces him or her to re-evaluate it.

How did Freud come by this belief? Partly, it evolved from his knowledge of castration fears in men, or more specifically threat of loss of the penis, which to the boy meant loss of genital sensation, and from an adult view, loss of the main thread of satisfaction, well-being, comfort, color and excitement in life. He was inattentive to the fact that the girl was inevitably aware of genital sensation, even though she did not possess a penis. Further, many women did indeed complain of this lack to him. Enmeshed in Victorian tradition, as all men are captives of their time, he failed to understand that this lack symbolized the underprivilege—economic, educational and social of his time and of his society. Although he believed all women suffered from the lack of a male genital, for those who had apparently great difficulty with their femininity, many of whom attempted to emulate men, he elaborated the concepts of penis envy and the masculinity complex.

In the evolution of psychoanalytic thinking, some, like Helene Deutsch, have clung to the classic concepts about the psychology of women, while others, notably Karen Horney and Clara Thompson, have pointed out that male and female are equal but different. Clara Thompson, in her papers, including "Cultural Pressures in the Psychology of Women," emphasized the cultural aspects of women's envy of men. Horney stressed the creative aspect of the female reproductive function, and the intimacy of the mother-child relation. In a paper entitled "Flight from Womanhood" in 1926, she said: "And what about motherhood, and the blissful consciousness of bearing a new life within oneself, and the inevitable happiness of the increasing expectation of the appearance of this new being, and the joy when it finally makes its appearance and one holds it for the first time in one's arms."

Freud made some further assumptions, based on his observations of women: that women are masochistic, that they have weaker superegos than men, that they are

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passive, especially in relation to sexual experience. These concepts also were derived instinctually, and not from the perspective of biological and socio-economic dependency. Certainly, observations of animal behavior do not point to female passivity.

Ford and Beach in "Patterns of Sexual Behavior" state:

"There is a widespread belief that male animals of most species almost always assume complete command of the mating situation, and inevitably play a more active role in courtship. Nothing could be further from the truth. Distribution of initiative varies from species to species; but in the main, the relationship is a reciprocal one in which both partners are sexually aggressive, and each contributes to the complete arousal of the other."

Furthermore, their observations indicate that among animal partners of any sex, the threatened animal frequently becomes passive and subservient, regardless of sex, the male frequently submitting to a female role. They quote Maslow, who asserts that primates which are subordinate may repeatedly show a sexual presentation to the partner, without the dominant animal necessarily making any response. Nevertheless, this gesture is frequently followed by permission on the part of the dominant partner for the subordinate to take food or to carry out some other activity that it would not ordinarily be allowed to perform. In addition, they state:

"Female macaques and baboons also assume the initiative in seeking intercourse while they are in oestrus, but in both of these species, dominant males demand and often receive sexual satisfaction from females that are not in heat and are not anxious to copulate. The feminine response in such cases has the appearance of submissive acquiescence to a potential enemy. Females of the spider and howler monkey groups, in contrast, have not been seen to permit coitus save when they were physiologically in oestrus. They do not employ sex as a social device to avoid injury by a male."

Carl Abraham in 1920, in a paper entitled "Manifestations of the Female Castration Complex," was perhaps the first to point out that certain phenomena were observable in women that pointed to the existence of a "castration complex" similar to that observable in men. He accepted and elaborated upon Freud's views here, as elsewhere. He said:

"Many women suffer temporarily or permanently in childhood or in adult age, from the fact that they have been born as females. Psychoanalysis shows that a great number of women have repressed the wish to be male. The girl does not recognize that her body exhibits a defect in comparison with the boy. Incapable of recognizing a primary defect in her body, she later forms the following idea: I had a penis once as boys have, but it has been taken away from me—a theory which we repeatedly come across. She therefore endeavors to represent the painfully perceived defect as a secondary loss and one resulting from castration. The female genital is looked upon as a wound, and as such it represents an effect of castration."

It must be evident that such a view holds no place for the vicissitudes of life which may affect a woman's attitude about herself.

Ernest Jones in 1927, in a paper called "Early Developments of Female Sexuality," brought a refreshingly new viewpoint to bear on the problem. He pointed out that females as well as males seem to experience a fear of castration, but he related it in the female to a lack of permissiveness on the part of adults in general, and the father in particular, for any sexual curiosity or sexual exploration in the child, or sexual behavior or intercourse in the adolescent or young unmarried adult. But he went beyond the concept of the female castration complex as something inevitably present in all women as a consequence of their biologic and instinctual inferiority, and related its presence to the attitude of adults, particularly the father, in relation to whom the girl's superego developed, in his view. He ignored the role of the mother, and his concept of what might prove traumatic in female development was limited to sexual prohibition, and did not take into account the damaging effect from other sources, on feminine development.

Recently, a view has been offered which defines the female castration complex as having two components: 1) The phallic component, which consists of the girl's recognition of the lack of a penis and her envy of the male, and 2) the feminine component, which consists of interference with, or injury or threatened injury to feminine development.

This definition is an attempt to straddle the fence, and retain Freud's original concept even while pointing out that the motive force for the castration complex may come from other sources. Earlier, Helene Deutsch attempted to reconcile Freud's original views with later data. She retained the passive, masochistic concept of femininity, but rejected the phallic component, or, the damaged self-image from lack of a penis, saying:

> "Penis envy is generally ascribed to the reaction expressed by the little girl when she first sees the masculine organ. It seems unlikely that a trauma of external and accidental origin should play a fundamental part in the formation of feminine personality."

However, she considered penis envy as being essentially determined not by external events, but rather instinctually. I would like to propose that the female castration complex, that is, the reaction to interference with, or injury to feminine development, is a complex of the interaction of significant persons, especially the mother, with the girl, as influenced by the cultural matrix. It can be inferred from this that it is potentially present in all women.

Freud recognized the complexity of female sexuality because of its duality. The first aspect of this concerns woman's role as sexual partner. Attitudes relating to it would be feelings of femininity and sexual desirability, and various nuances pertaining to the wifely role. The second aspect concerns woman's reproductive function and her maternal attributes. These encompass that part of the self-image which contains feelings of being a giving, loving, protective person. Inevitably, the two aspects of female sexuality are interrelated, yet the attitudes in one area do not necessarily reflect the attitudes in another. I have known women who have experienced grave difficulties in the area of femininity and sense of sexual desirability, who nonetheless, having been given the opportunity of motherhood, have blossomed in the experiencing of their maternal function. On the other hand, I have known women who, although assured of femininity and desirability, have conveyed a tragic sense of barrenness and failure as a result of their inability to have children.

There are certain milestones in life at which we stop to survey the road we've travelled, and also glimpse the road ahead. We stop at these points because they are of physiological, biological or social significance. For the woman, the onset of menstruation, marriage, pregnancy (especially the first), divorce, menopause are such times. All of these mobilize feelings about the self, and inevitably the self as woman. The onset of menstruation focuses on attitudes relating to feminine sexuality. It is the start of the reproductive function and also contains a summation of all the feminine feelings and attitudes to that point. It is something experienced by every girl at approximately the same time, and memories relating to this experience frequently contain a few drops of the distillate of the mother-daughter relationship. I will give a brief example from the analysis of a 40-year-old woman:

> As an 11-year-old girl with no preparation for her menses, she awoke early one morning feeling wet. She threw off her bed clothes, and on observing that she was covered with blood, ran in panic to her mother's room. Her mother greeted her with a show of annoyance, slapped her face, then said this was a natural occurrence, but it really should *not* have come on for another year or two. She was told what to do for herself hygienically, advised to take to her bed for the day, but given no other information. At 14 she had the following experience: She had been the favorite grandchild of her maternal grandfather, an orthodox Jew. Upon his death, she was denied admission to the cemetery to participate in the burial ceremony. She was told that a menstruating woman is unclean and cannot set foot on holy ground. Thus, not only was she cut off from her grandfather by death, but from the last meaningful experience in relation to him, and a structured occasion to work out her grief. She developed a deep feeling of resentment about being a girl. It seemed to her that people viewed a girl as a sickly, inferior creature, and her function of menstruation as something undesirable and abasing. Here we can see directly the cultural aspect of her self-devaluation as a woman, and the role of her mother and social group in contributing, in these instances, to its development.

Time does not permit discussion in detail of a study I have undertaken, focusing on the circumstances of the menarche, those aspects of the mother-daughter relationship

revealed by it, and the subsequent menstrual difficulties which ensue, and are, I believe, a direct consequence of early experiense—allowance being made, of course, for physiological factors. But I would like to call attention to some conclusions from this pilot study of 103 women: Of the total, in only 15 instances had the mother adequately prepared the daughter for the onset of menstruation, and received the news of its occurrence with joyful recognition of a new step along the road to maturity. Of these fifteen, 13 were free of any symptom of premenstrual tension, these being the only women free of premenstrual tension in the total group. Symptoms of premenstrual tension, and to some extent dysmenorrhea, are directly related to unpleasant, humiliating, or unloving experience in relation to the mother. Premenstrual symptoms fall into two main reactions—1) those relating to helplessness and need for love—such as hunger, wish to call mother, depression; and 2) those relating to defensiveness against anticipated attack, such as irritability, quarrelsomeness, headache, nausea and vomiting. These symptoms are a constant compulsive recapitulation of devaluation of the self in relation to femininity.

To summarize, the following points were covered:

1) Freud's views on the psychology of women, particularly his concepts of biologic and instinctual inferiority of the female, represented by the lack of a penis, and evidenced by female passivity, masochism, weak superego structure, penis envy, masculinity complex and castration complex were reviewed and challenged.

2) It is proposed that the same phenomena can be better understood from a consideration of cultural factors.

3) Data was referred to—from a study of menstruation, as one area contributing significant developmental information about the psychology of women.

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Use of Thioridazine (Mellaril) in Psychological Disorders

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Thioridazine is 2 methylmercapto-10-[2-(N-methyl-2-piperidyl)-ethyl]-phenothiazine hydrochloride. Its most notable difference from chlorpromazine is the presence of a thiomethyl radical ($S\text{-}CH_3$) which may be responsible for the relative absence of side effects. We have used this compound for nearly two years on over 200 patients. We are reporting results in the first 125 of these. We have been concerned to a) establish dosage; b) note any side effects; c) estimate efficacy as based on clinical response primarily in schizophrenia.

Method

Subjects: There were 125 subjects of whom 105 were female and 20 male. The predominance of females is an artifact due to one author running a female service.

Schizophrenia: There were 84 patients from 16 to 79 years of age of whom considerably over half (52) were aged 45 or younger; 32 were suffering from acute or sub-acute illness with presenting symptoms of less than two months' duration, and the remainder with symptoms of variable duration up to 40 years. More than a quarter in this or a previous illness had received chlorpromazine.

They were classified as:

40 paranoid
27 catatonic
14 undifferentiated (this included 2 with puerperal psychosis in a predominantly schizophrenic form)
3 persistent childhood schizophrenia

Non-schizophrenic Illness: There were 41 patients, the majority under 45, with an age range of 21 to 78. There were 26 females and 15 males. Diagnoses were as follows:

4 psychoneurotic reactions (anxiety phobia predominating)
4 personality trait disturbance, passive-aggressive (usually complaining of 'anxiety')
11 manic depressive conditions:
  3 depressed
  8 hypomanic
11 alcohol addiction (admitted for 'drying-out')
6 chronic brain syndrome (2 associated with brain trauma, 2 post-encephalitis lethargica)
5 mental defective

In all patients the severity of their symptoms had been sufficient to require admission to hospital and all were initially treated as in-patients. The majority were admitted to a mental hospital and the remainder to a general hospital.

Dosage: Usually the compound was commenced in a dosage of 50 mg. four times a day and the 24-hour dosage range was 100 to 3200 mg. We usually increased this dosage rapidly to 400 to 600 mg. within 24 hours. This was maintained to alleviate symptoms.

Results

Outcome was judged by the following:

SCHIZOPHRENIA:

Recovery: Complete remission of symptoms with discharge from hospital and return to pre-morbid activity. We wish to stress that, in our opinion, this may be regarded as a "remission" rather than recovery.

Much Improved: Marked improvement of the thought disorder and affective impairment of the patient, usually with associated improvement of volition and secondary symptoms of delusions, hallucinations and motor disturbance.

Improved: A marked reduction of primary and secondary symptoms of schizophrenia. There was also greater tractability and ease of management with usually greater participation in hospital life.

Unchanged and Worse are self-explanatory.

NON-SCHIZOPHRENIC ILLNESS:

Recovery: As above.

Much Improved: A significant reduction of symptoms, usually associated with discharge from hospital and return to approximate pre-morbid activity.

From Queen's University and Ontario Hospital, Kingston, Ontario, Canada.

The drug, thioridazine, used in this study was kindly supplied by Sandoz Pharmaceuticals, Dorval Station, P.Q., as Mellaril.

Improved: Some reduction of symptoms, to a non-incapacitating degree.

Unchanged: Continuing incapacitating symptoms which did not necessarily require in-patient care.

SCHIZOPHRENIA: 20 recovered, 22 were much improved, 39 improved, 3 were unchanged and none were worse (see Table I). The paranoid schizophrenias showed a greater degree of improvement when compared to the catatonic and undifferentiated variety.

NON-SCHIZOPHRENIC ILLNESS: 4 recovered, 1 much improved, 28 were improved and 8 were unchanged (see Table II). The recoveries were all from hypomanic illness. For example, one married lady of 34, who had suffered from recurrent hypomania, had in her previous admissions been controlled only with the greatest difficulty by a combination of multiple electroconvulsive therapy and chlorpromazine. In her present illness thioridazine was rapidly increased to a daily dosage of 2400 mg.; later reduced to 900 mg. which made it possible for her to remain on an open ward. The duration of her exacerbation, some ten weeks to remission, was not shortened, but we considered that the therapy was, if "non-specific," certainly more elegant and desirable for patient and staff.

One mentally defective patient whose superimposed psychosis remitted sufficiently to allow her probation was regarded as much improved.

The improved patients included the alcoholics in whom the drug brought about a quiescent drying-out period. The remainder of improved cases included the chronic brain syndromes and mentally defective patients in whom impulsive disturbed behavior was considerably lessened. Amongst the unchanged patients were three cases of manic depressive depressed illness who later responded to ECT. Only three of the patients with psychoneurotic illness and pathological personality trait disturbances were regarded as improved and these not greatly.

Effect of the Drug

We found that the drug was an efficient "tranquilizer" which produced greater tractability in all patients showing disturbances of motility. Of the primary disturbances of schizophrenia, thought disorder was frequently markedly improved, with an accompanying lessening of the disturbance of affect, although at times this remained flattened or inappropriate. Such change was usually accompanied by greater volition and purpose, although occasionally quiescence of the turbulence of the illness seemed to be

TABLE I
Outcome and Diagnostic Sub-Group in Schizophrenia

Type	Number	Recovered	Much Improved	Improved	Unchanged
Paranoid	40	15	10	14	1
Catatonic	27	3	5	18	1
Undifferentiated	14	2	6	5	1
Childhood	3	0	1	2	0
Total	84	20	22	39	3

TABLE II
Outcome and Diagnostic Sub-Group in Non-Schizophrenic Patients

Type	Number	Recovered	Much Improved	Improved	Unchanged
Psychoneurotic	4			2	2
Pathological personality	4			1	3
Manic-depressive depressed	3				3
Manic depressive-hypomanic	8	4		4	
Alcoholic	11			11	
Chronic brain syndrome	6			6	
Mental defective	5		1	4	
Total	41	4	1	28	8

TABLE III
Symptomatic Response to Thioridazine

Type	Excellent	Good	Moderate	Poor
Schizophrenia	×			
Anxiety				×
Depression				×
Hypomania		×		
Hypermotility		×		
Alcoholic Withdrawal Syndrome		×		

marred by a persisting anergy. Complacency and hebetude led to a reluctance to engage in either pleasures or chores of hospital life and even less desire to contemplate a return to home or job. Delusions, hallucinations and catatonic phenomena were always favorably influenced. In our experience, psychoneurotic anxiety was usually not very favorably influenced and certainly not quieted to the degree produced by barbiturates.

Dose Level Effects and Combination With Other Drugs

Our impression was that the milligram potency of thioridazine was equivalent to, if not somewhat higher than chlorpromazine. However, it is a difficult question to decide in view of the absence of side effects with thioridazine. Thus, one of the habitual methods of prescribing phenothiazines in schizophrenia has been to "tolerance," i.e. until the onset of parkinsonism. This manifestation in turn is treated with anti-parkinsonian drugs. The absence of such readily apparent index may have led to use of greater dosage. However, this was considered to be a factor in favor of thioridazine, namely that the dosage could be increased to control the disease without polytherapy. The qualitative response in schizophrenia in those patients who had previously received chlorpromazine was similar but a number had had severe parkinsonian symptoms on the dosage level necessary to control their illness.

After the first week or two the drug was usually prescribed in a single daily dose of from 200 mg. to 1000 mg., the majority receiving 500 mg. Like all phenothiazines, thioridazine may, and perhaps preferably should be, administered in a single daily dose in schizophrenia. The gain of nursing time in a mental hospital is noteworthy.[1] We experimented with the enteric coated capsule but found that this had no advantage to offset its increased production cost. The side effects of hypotension were in fact as frequent with the enteric coated as with the non-enteric coated tablets. (Both of course, being somewhat minimal and not incapacitating.) The striking multi-colored appearance of the enteric coated tablet however had a marked effect on some of the patients, illustrating the non-specific factors that enter into the administration of a drug. One nurse was convinced that her patient was improving when she was on the "beautiful multi-colored tablets," whereas she was going steadily downhill on the same dose of the plain colored compound. This impression was not shared by the doctor.

Although in some excited restless patients we have combined thioridazine with a night sedative such as amylobarbitone up to 800 mg., we have been increasingly impressed by the value of a larger evening dose of a phenothiazine alone to produce nocturnal tranquility. Our impression is that this phenothiazine has an additive rather than a potentiating hypnotic effect with barbiturates.

In some instances the drug was combined with imipramine, most notably in the two puerperal schizophrenic-like syndromes. Although very occasionally thioridazine seemed to benefit depressive illness (not here reported), the converse occurrence, namely a depression—appearing for the first time or becoming manifest only after the initiation of thioridazine therapy—was noted. In such patients, imipramine was added with beneficial results; 1400 mg. of thioridazine in one woman whose weight was 120 lbs. was combined with 600 mg. a day of imipramine without untoward results, and eventual improvement to complete recovery.

Side Effects

Transient giddiness due to postural hypotension was observed in some 5% of the patients, both schizophrenic and non-schizophrenic. This was seldom troublesome and was found to occur with the enteric coated capsules as well as the non-enteric coated ones. However, 4-hourly blood pressures revealed no sustained hypotension.

Serial liver function tests were done in 25 patients at weekly intervals. Serum bilirubin, alkaline phosphatase, serum transaminase and thymol turbidity levels remained unchanged. Routine urine and blood counts also revealed no abnormality.

One case of transient galactorrhoea in a woman of 30 was noted. On a dosage of

3200 mg. a day, one patient developed a coarse tremor of a faster frequency than a parkinsonian one. This faster frequency might be indicted as a basal ganglionic disturbance without the dampening effect of increased muscle tone. However, only two cases of parkinsonian rigidity with mask-like facies but without salivation have been observed. Both were receiving more than 1000 mg. of thioridazine a day, were not part of this series and will be separately reported. Thus, extrapyramidal symptoms were extremely rare.

Some patients complained of lassitude and in 10% this became aggravated into the anergy which we have already described and which in some was associated with a considerable gain of up to 10% or 20% of body weight. In a number of such patients after initial improvement with thioridazine, we have switched to perphenazine with, to date, encouraging results. However, the mechanism remains obscure and we would hesitate to generalize from this experience.

We have not been impressed with the suggestion that the high mg. potency phenothiazines such as perphenazine and trifluoperazine have a specific "energizing" effect on retarded schizophrenic patients. This would seem to us to be more a function of the dyskinetic phenomenon of acathisia, which propels a patient into movement but which is probably a phenomenon unassociated with schizophrenic illness or its improvement. An alternative and simpler explanation for the response of "previously refractory" schizophrenic patients to such compounds might be the greater likelihood of a therapeutic dosage being used. Homeopathic dosage of phenothiazines is all too common in our experience.

Safety of the Drug: As an illustration of the safety of the drug in a single dosage, one old lady of 90 years who was on no other drugs was, by mistake, given 400 mg. in one dose and survived with no discomfort.

Discussion

We considered that although there did not seem to be any specificity of thioridazine, it presented in contrast to chlorpromazine, significant advantages due to its greater safety, its ability to be administered in a single very large dose and in its almost complete freedom from side effects. Thus, economy of treatment like economy of hypothesis remains a desirable goal. We consider that it is better to prescribe one drug if its action is as good, rather than two (i.e. a phenothiazine plus an anti-parkinsonian drug) to achieve the same result. In a number of cases the dosage of thioridazine, i.e., between two and three thousand milligrams, and could be administered without side effects or discomfort and enabled patients to be controlled and improved in a way that had not been possible with any combination of medication prior to the advent of this drug.

We wish to stress, however, that dosage should be carefully adjusted to clinical response. Thus, the very safety of this drug and freedom from side effects may lead the unwary into injudicious over-dosage. Although as yet no apparent ill effects may accrue, we consider such a therapeutic regime potentially dangerous. We would urge minimal dosage compatible with clinical improvement.*

We found only isolated cases where it benefited depressive illness and this remained true in our experience with all phenothiazines. Its mode of action in these cases is anomalous and as yet unexplained.

Hypomanic and restless disturbed mentally defective patients were well controlled by this means. The drug was useful in the management of acute alcoholism, although the absence of a parenteral preparation, as noted by Azima, et al.,[2] remains a handicap.

In schizophrenia, the drug appears to be active on primary symptoms but may lead in some to secondary anergy. The precise determinants of this condition have not yet been worked out. We plan to make more careful behavioral ratings of patients and their response to the drug.

The advent of an effective phenothiazine which does not produce significant secondary parkinsonian effects may lead to a refor-

*Since writing this paper, May, et al.,[5] have reported pigmentary retinopathy in four patients each having received a total dosage in excess of 85 GM.

mulation of the aetiological role of the basal ganglionic system in schizophrenia.[3] This hypothesis has always seemed somewhat illogical to us. The presence of a *dysfunction,* for example noise from a defective engine, would scarcely lead to the interpretation that its *function* is the *suppression* of noise.

Finally, the relative value and specificity of thioridazine as an "anti-schizophrenic" agent must stand the test of time. In our opinion, only chlorpromazine has to date been thus validated. We are still, however, too ignorant of some of the behavioral parameters of the illness—such as the presence or absence of over-inclusive thought disorder[4]—to be dogmatic in our choice of drug. These areas are awaiting exploration.

Conclusion

Thioridazine has proved to be a safe, potent and efficacious phenothiazine with a minimum of side effects. Improvement of primary symptoms in schizophrenia may be followed in some patients by a secondary anergy. This may respond to other high mg. potency phenothiazines.

Extrapyramidal signs are extremely rare.

The drug seems to present a definite advantage over chlorpromazine, enabling control to be achieved without incapacitating parkinsonian side effects. It also represents an economy of therapeutic action obviating the need for a second drug to combat these side effects.

To date, it appears to be effective in schizophrenia, but its specificity and comparative value must await clearer behavioral correlates.

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Amitriptyline in the Treatment of Depressive States

(A Pilot Study)

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What is the enigma called depression? This question continues to arise partly because of the present type of classification of psychiatric diseases, since the categories are undifferentiated and primitive. The Kraepelinian system remains basically unchanged and are not meaningful for the formulation of a dynamic etiological psychopathology. Our ability to diagnose, treat and discover more effective drugs for neuropsychiatric disease rests on our acumen in defining homogeneous categories based on symptoms and signs (phenomenology). In treating a phenomenon as common as the depressive state, with its many manifestations of aberrant affect, a comprehensive biological approach is required.

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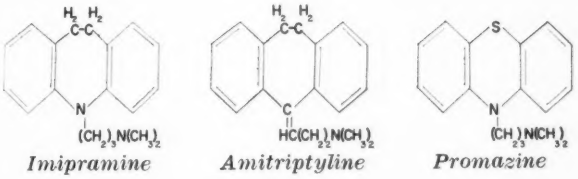
Depression in psychiatric usage continues to have different meanings. It is referred to, both as a symptom and a disease entity. Its diagnostic value is limited because of the fact that it is used alternately to describe a mood, a symptom, a syndrome or a disease entity. The etiology of a depression of affect remains unknown and the psychodynamic formulation of depression remains unacceptable since it fails to meet scientific criteria. It becomes obvious that a concise definition of depression does not exist since it may occur in all neuropsychiatric diseases with their probable multiple etiological factors.[1] We believe it essential to state that the symptoms of depression may be classified by phenomenology as primary and secondary according to Blueler's description of schizophrenia. The primary symptoms of depression include melancholia, sadness, de-

spair, dejection, a dearth of psychic energy and mental productivity as indicated by fear of initiating new activities, and psychomotor retardation or agitation. The secondary symptoms are characterized by delusions of persecution, feelings of depersonalization, hypochondriacal complaints, obsessive-compulsive behavior, hallucinations and suicidal tendencies. Accompanying these psychic symptoms are frequent signs of visceral autonomic, endocrine and metabolic dysfunction attributable to the limbic system.[2,3] Specifically these signs are anorexia, constipation, dryness of mouth, insomnia, a reduction of menstruation in women, and a tendency to impotence in men.

Depression continues to create a semantic problem among the psychiatrist, psychologist and physiologist which will remain until the etiopathological mechanisms of affect are known. William A. White wrote, "The whole question of the differentiation of some cases of manic-depressive psychosis from dementia praecox involves the greatest nicety of observation, interpretation and judgment." This difficulty is magnified because in practice nosological rather than phenomenological classification is usually used. Clinical studies with known and experimental phrenotropic drugs support this concept because they alleviate or ameliorate both primary and secondary symptoms in varying degrees in neuropsychiatric diseases. Diagnosis and treatment of depressive states must be based on their primary symptoms; otherwise the incidence of exacerbation of these symptoms is increased.

The pharmacological treatment of depressive states has been frequently accomplished with monoamine oxidase inhibitors[4-7] and to lesser degrees with imipramine,[8] deanol[9] and procaine.[10] This report is on the use of amitriptyline as an antidepressive agent in psychotic patients. Amitriptyline is an isostere of imipramine which is an isostere of promazine. These chemical changes in the B ring of the phenothiazine molecule produce structural differences between the molecules that seem to be responsible for their biologic differences. The mechanisms of linking these compounds in vivo for the production of the complex essential for their biologic avtivity remain unknown.

Amitriptyline is chemically 5-(3-dimethylamino-propylidine)-dibenzo (a, d) (1, 4) cycloheptadiene hydrochloride. It is structurally related to imipramine within the limitation inherent in all molecular models as both have nearly the same spatial volume, angles between the components of the ring systems, and the relationship of side chains to the seven-membered rings. The physicochemical property of electron densities in the area of the points of attachments of the side chains are similar. It is water soluble (20 gm. per 100 ml.) and has a molecular weight of 313.85.



Imipramine *Amitriptyline* *Promazine*

Patient Selection: The patients selected for this preliminary study were 19 white female psychotics between the ages of 50 and 90 years. Duration of hospitalization at the start of therapy was from 1 to 4 years for 7 patients, 5 to 10 years for 7 patients and over 10 years for 5 patients. All had received previous pharmacological, insulin or electrocoma therapy with little or no clinical improvement. The patients were selected on the basis of the primary symptom, depression; they frequently demonstrated other primary and secondary symptoms.

Dosage: Amitriptyline was started at 25 mg. t.i.d. orally and increased 25 mg. per day to a maximum dose of 75 mg. t.i.d. if there was no improvement. After three months of oral therapy, 10 mg. t.i.d. was given intramuscularly and one patient later received 20 mg. b.i.d. for two months. Amitriptyline was given to 15 patients for 5 months and 10 patients received it for a minimum of 7 months. Preliminary indications are that 75 mg. per day provide an effective dose.

Results

The alleviation of depression was significant between the second and sixth week although clinical improvement began the

TABLE I

Distribution of Patients

Phenomenology	*No. Pts.*
Depression	19
Aberrant Affect	19
Inertia	16
Agitated Depression	1
Suicidal	4
Mutism	6
Delusion or Hallucination	4
Confusion	5
Untidy	3
Nosology	
Manic Depressive, Depressed	6
Psychosis with CAS	4
Schizophrenia, Paranoid	3
Schizophrenia, Catatonic	1
Schizophrenia, Schizoaffective	1
Senile Psychosis	2
Involutional Psychosis, Melancholia	2

first week. There was marked improvement (alleviation of depression) in six of the 19 patients after six weeks' therapy. Improvement in two of these patients occurred during the first two weeks; in two more within three weeks and in the remaining two between four and six weeks. There were four patients who were cyclic in their response; that is, they were relieved of their depression but it returned with less intensity. In five patients there was no change with both oral and intramuscular amitriptyline therapy. We discontinued amitriptyline in four of the 19 patients; one had a rise in alkaline phosphatase from 5 to 11 Bodansky units during the second month, one had a rise in blood urea nitrogen (BUN) from 19 to 31 mg. during the first month with increased restlessness, another had marked vertigo on the fourth day and refused the medication; the fourth patient had a mild coronary attack, the cardiogram indicating marked insufficiency.

These early favorable responses were maintained by continued medication with occasional daily fluctuations during the initial period of five months. It must be emphasized that amitriptyline did not produce exacerbation of the symptoms of psychoses such as occasionally occurs with imipramine and the monoamine oxidase inhibitors, and it has weak antipsychotic effect.

We have continued 10 patients on amitriptyline for another two month period, one patient, a 90-year-old discharged patient on convalescent status and the nine remaining in this hospital. Three of these hospitalized patients have shown considerable improvement during the last two months of therapy and in three the improvement in their depression was slight. It appears that continued medication reduces the cyclic depressive phenomenon both in intensity and frequency and we suspect further amitriptyline may eliminate it altogether in many cases. It is probable that therapy must be continued for many depressed patients as it is in many of the known metabolic diseases of man such as insulin for diabetes mellitus. The dosage for this additional two month period was 75 to 150 mg. per day orally or 20 mg. intramuscularly. Three patients showed no improvement but there were no untoward reactions to additional therapy.

Our observations indicate that depression may be alleviated or ameliorated in schizophrenia and other psychoses by amitriptyline. This was demonstrated by changes in the repetitive, purposeless thinking of the psychotic patient with a more responsive form of communication resulting. Flattened affect was replaced by an increased sensitivity and reactivity that was cyclic at times but free of the schizoid quality. We have observed the clinical efficacy of combination amitriptyline and phenothiazine therapy and found it to be especially useful as an adjunct in the treatment of schizophrenics who manifest symptoms other than depression.[11] Amitriptyline therapy is suggestive of the results obtained from the combination of a monoamine oxidase inhibitor plus a tranquilizer in improving communication and purposeful acts in the autistic patient.[12] Amitriptyline is an effective antidepressive agent and possesses in addition, other antipsychotic activity, that is, it is able to ameliorate primary and secondary signs of depression and of schizophrenia with varying effectiveness.

Side Actions

The most interesting phenomena in this preliminary study are the absence of psychotic exacerbations and seizures with ami-

triptyline which are occasionally experienced with other phrenotropic drugs. The central nervous system actions are indicated by the vertigo, increased listlessness and weakness, each of which was experienced by one patient receiving the drug. There were no significant hypotensive effects but one patient, after one month's therapy, had an electrocardiogram indicative of insufficiency. We have not observed any extrapyramidal signs. In another study[11] two patients felt weak and dizzy during the first three days of therapy and one patient became euphoric on 25 mg. t.i.d. but this was controlled by reducing the dose to 25 mg. b.i.d. Routine urine analysis, CBC and hematocrit are all within the range of change observed in this hospital in the absence of phrenotropic drugs. There were transient rises in BUN in 10 patients during the first month, followed by a return to a normal level during the remaining course of therapy with one patient's BUN increasing from 19 to 31 mg. when the drug was discontinued. Both SGO and SGP transaminases and the alkaline phosphatase remained within the normal range of activity and these were followed monthly.

Discussion

Presently available antidepressive agents may exacerbate the signs and symptoms of a psychosis. Both the monoamine oxidase inhibitors and imipramine, to a lesser degree, will produce this untoward effect. This led us to administer simultaneously a tranquilizer and an energizer,[4,12] in order that both primary and secondary symptoms could be controlled more effectively. It is of great interest that amitriptyline has a good clinical efficacy in controlling both groups of symptoms but its principal action in psychotics is antidepressive.

Pharmacologically this preparation differs from the monoamine oxidase inhibitors and central nervous system stimulants in that many of its actions may be considered depressive, like the phenothiazines, rather than antidepressive. There is no known pharmacologic basis for the therapeutic efficacy of amitriptyline. We speculate that its effect is by sensitization and activation of central adrenergic mechanisms chemically at the submolecular level.

The experimental animal pharmacology failed to reveal any significant indication that amitriptyline would be effective as an antidepressive; this again confirms the need for human pharmacological studies if the therapeutic efficacy is to be known. Amitriptyline has central nervous system effects similar to chlorpromazine but of varying intensity when compared to a specific function.[13] Its anticonvulsant activity in mice was about equiactive to diphenylhydantoin against the tonic extensor component of electroshock and pentylenetetrazole. In part, the significance of this action is the absence of seizures in patients receiving this preparation; the phenothiazines and imipramine produce seizures, the akinetic type with the latter drug. The electroencephalographic effects of amitriptyline in cats and monkeys are similar to those associated with the administration of chlorpromazine and imipramine.[13]

Amitriptyline exhibited sedative-like effects in monkeys working under an avoidance schedule. While the ability of the animals to avoid an aversive situation was reduced, amitriptyline had little effect on the capacity to escape the aversive stimulus. Monkeys have shown instances of increased rate of lever pressing on avoidance with amitriptyline and imipramine but this is less characteristic with chlorpromazine. Since this function has also been noted with scopolamine, it is probably an anticholinergic effect of the central nervous system. The fixed interval response was also modified. However, changes such as the temporal patterning of responses in the fixed interval behavior were not seen with chlorpromazine and only slightly with imipramine. Amitriptyline resembles imipramine in the following respects but in each response it is significantly more active: a) It has anticonvulsant effect as indicated by the modification of the electroshock seizure pattern and pentylenetetrazole-induced convulsions. b) It has an effect on the autonomic nervous system as indicated by its potent antihistaminic activity, weak peripheral anticholinergic effects

and some capacity to antagonize the vascular action of serotonin and epinephrine in dogs.

Clinically, when amitriptyline was used alone or in combination[11] we found a very low incidence of signs and symptoms attributable to the autonomic nervous system. We believe the reports of high incidence in many studies are due to the lack of recognition that these signs and symptoms exist as part of the depressive state and for this reason we classified them as to primary and secondary symptoms and into three groups of signs. Amitriptyline apparently has little peripheral anticholinergic effect in man. A central nervous system component may be operating, however, as is indicated by the increased rate of lever pressing on avoidance in monkeys. The antihistaminic activity of amitriptyline in man remains to be determined because the role of histamine in the brain is not clear but it is known that the hydrazine monoamine oxidase inhibitors shift the metabolic route in man.[3,4,7,14] The antiserotonin activity is significant in the dog and this was accompanied by a parallel decrease in epinephrine pressor response and by a minor increase in the norepinephrine pressor effect. The weak inhibitory actions on the adrenergic effector indicate that amitriptyline will probably produce few symptoms referable to this blockage and we have observed no directly attributable cardiovascular actions. Imipramine, on the other hand, does not reduce epinephrine pressor effects and produces greater potentiation of norepinephrine pressor actions. Imipramine's distribution in the rabbit heart muscle is relatively high as compared to ordinary muscle,[15] and we had serious cardiovascular difficulties in several geriatric patients.

Amitriptyline is a drug of many functions in the central nervous system, stimulating some while depressing others. The therapeutic mode of action is not revealed by experimental animal studies, by its clinical efficacy in relief of depression, nor by its side actions. The antidepressive action does not coincide with nosological groups nor can our preliminary findings be correlated with psychopathological factors. We hope the clinical efficacy of amitriptyline will stimulate further investigations in order that its mechanism in freeing the patient of his depression may be determined.[16]

Conclusions

1. Our observations and opinion from this pilot study with amitriptyline led us to conclude that it is an effective and safe antidepressive for treatment of depressive states.

2. The etiology and mechanism of depressions remain unknown as are the pharmacological effects responsible for the clinical efficacy of amitriptyline. We speculate that amitriptyline functions biochemically at the submolecular level to sensitize and activate central adrenergic mechanisms but all its central autonomic system actions must be suspected as contributing factors.

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Fluphenazine in the Treatment of the Hospitalized Psychiatric Patient

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Introduction

Chlorpromazine, the first of the phenothiazine tranquilizers, has been the impetus for numerous phenothiazine derivatives in the search for more potent tranquilizers. These derivations have followed two main channels—a change in the halogen attached to the phenothiazine nucleus or an alteration in the configuration of its attached side chain. It has been observed that separately or in combination fluorination and the utilization of the piperazine ring in the side chain have increased the potency of the drugs in terms of the criteria proposed by Freyhan[1]: (a) the attainable level of psychomotor inhibition; (b) the speed of action; and (c) the dosage required to obtain effective action. It was reasonable to expect that fluphenazine, whose chemical structure includes both a fluorine and piperazinyl component, would possess highly potent properties. This was verified by the studies of Ayd[2] and Darling.[3] These investigators found fluphenazine at least twice as potent as trifluoperazine (Stelazine) milligram for milligram, three to five times as potent as perphenazine (Trilafon), and ten to twenty times as potent as chlorpromazine (Thorazine). They also found an increase in its speed and duration of action with a minimum of sedative, autonomic or endocrine side effects.

Unfortunately the potency (in terms of dosage) of the phenothiazine derivatives is not always a clear indication of their therapeutic effectiveness since there is not always a one to one relationship between potency and effectiveness. Indications from a recent clinical study by Niswander and Karacan[4] are that fluphenazine is not only a highly potent drug but also an effective tranquilizing agent. This present study is an attempt to evaluate fluphenazine's effectiveness in a more controlled manner since preliminary investigations have so far been encouraging. It is also our plan to investigate concurrently the problem of regressed behavior in hospitalized psychiatric patients as it relates to treatment with the phenothiazines.

Population Characteristics

The sampling of patients selected for study consisted of those patients from a 375 bed male continued care service who had been on phenothiazine medication for at least one month. Such patients were considered suitable candidates for a new phenothiazine since staff psychiatrists had already prescribed similar, albeit less potent, medication for them. This selection procedure assumed, of course, that the staff psychiatrists had originally placed the patients on phenothiazine medication on the basis of sound clinical judgment.

At the start of the study 55 patients were on phenothiazines, 38 on chlorpromazine, nine on perphenazine, nine on prochlorperazine, and one on promazine. Two other patients receiving additional medication along with phenothiazines were excluded from our study. It was possible to follow 24 of the original group of 55 patients through the subsequent experimental phases, and it is on these patients that the analysis of results is based. Of the 31 patients who failed to complete the project, two were considered to be unratable on the evaluation instrument used (these two patients were followed clinically, with no change noted in their status); three developed complications on their original medications before baseline evaluations were obtained; two developed complications while on fluphenazine (sore throat and fever in one case and leukopenia in another); 17 patients were either transferred from the service or

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Fluphenazine supplied as Prolixin by the Squibb Institute for Medical Research, New Brunswick, New Jersey.

paroled before the fluphenazine treatment stage was reached; and seven were dropped because of scheduling difficulties.

The age range of the 24 patients completing the project was from 20 to 64 years, with a mean age of 40 years. The patients had been in the hospital from 5 to 24 years, with a mean length of hospitalization of 13.5 years. The degree of normality for this group was determined in terms of the Multidimensional Scale for Rating Psychiatric Patients (MSRPP).[5] The chronic nature of the population necessitated the use of a MSRPP "normality" score instead of the usual "total morbidity" score which is unduly influenced by the number of unratable items comprising the various MSRPP subscores. Since the normality score is less influenced by the unratable items and since the correlation between normality and morbidity was found to be —.94 for this population, the former score was utilized. The mean "total normality" score was 26.04 compared to the MSRPP's estimated mean normality score of 31.00 for the normative psychiatric population. (The over-all range for total normality, which includes both ward and interview observations, is from 0 to 62, with higher scores indicative of less pathology.)

Method

A clinical evaluation of the degree of illness of these patients was made initially by a research psychiatrist who subsequently saw the patients in brief, semi-structured interviews throughout the study. The interviews were held at bi-weekly intervals unless marked changes in the patient's clinical state necessitated a need for making a decision relative to the institution of drug treatment.

The research psychiatrist was also responsible for the regulation of the various treatment phases. In consecutive order these were: (a) a control treatment phase, in which the patients were kept on their original medications; (b) a drug-free phase; (c) a placebo phase; and (d) a final fluphenazine treatment phase. The research psychiatrist was at liberty to initiate fluphenazine treatment during the drug-free and placebo phases whenever it was his opinion that the patients' behavior had become so regressed that immediate drug treatment was again considered necessary. Since it was desired to interfere minimally into the operational setting of the service, ward psychiatrists were responsible for the administrative handling of the patients although they were not informed of the medication schedules.

Patients were considered regressed clinically when there was an increase in aggressive acting-out behavior, increased excitement, or an intensification of delusional, hallucinatory, or autistic behavior. Usually such behavior prompted ward personnel familiar with the patients' patterns of reactivity to request that some change in treatment be made and these requests were usually acted upon by the research psychiatrist. Regression as defined here in terms of exacerbation of target symptomatology was not always associated with heightened MSRPP ratings, which measured internal dimensions of psychopathology as well as overt behavior.

The behavior of the patients was also observed and rated on the MSRPP at the beginning and end of each treatment phase by a psychologist and ward personnel. All treatment was administered on a code basis so that ward personnel had no indication whether the patients were receiving placebos or fluphenazine, although they were necessarily aware of the original medications and the following drug-free intervals. The psychologist responsible for the MSRPP interview ratings was not informed of the patients' medications at any time during the study nor was he aware of the basic design of the study. Besides the regular sequence of ratings originally set up, ratings on the MSRPP were also made whenever the patients' behavior became so regressed that immediate treatment with fluphenazine was necessary. The spacing and sequence of ratings were, therefore, not the same in every case since a certain percentage of the patients regressed during the drug-free and placebo phases.

For control purposes, the patients were

kept on their original medications for approximately eight weeks. The patients' medications were then discontinued for periods of time ranging from four to eight weeks, or until such time as their behavior was considered by the research psychiatrist to have become so regressed that treatment measures had to be reinstated. At the end of the drug-free period, or at times of regression, whichever came first, the patients were placed on medication—those patients who completed the drug-free phase without regression were placed on placebos, while those who regressed were placed directly on fluphenazine. The patients who had not yet regressed were then kept on placebo medication for a period of eight weeks, or, again, until such time as regressed behavior necessitated the patients being placed directly on fluphenazine. After the initiation of fluphenazine treatment all of the patients were kept on the drug for a period of eight weeks.

The sequence of MSRPP observations for the non-regressed patients was the following: initial baseline evaluations made while the patients were on their original medications, an evaluation made at the end of a four to eight week drug-free period, an evaluation at the end of an eight week placebo period, and a final evaluation at the end of an eight week fluphenazine treatment period. For those patients who regressed the sequence was: initial baseline evaluations, followed by an evaluation at the time of regression and a final evaluation after eight weeks of treatment with fluphenazine.

Fluphenazine was administered in capsules containing 1 mg., 2:55 mg. and 5 mg. for the first, second and third day of administration, respectively. The dosage for the majority of patients from then on was 5 mg. Q.D.; with only a few patients was it necessary to increase the dosage above this level. The highest dosage administered was 10 mg. T.I.D. The placebo was a matched capsule and was administered on a Q.D. basis. To those patients who refused to take their medications orally, ampule preparations containing 5 mg. were given intramuscularly. These were discontinued as soon as it was possible to administer the medication orally.

Initial laboratory data consisted in all cases of a routine urinalysis and blood studies comprising: blood urea nitrogen, blood glucose, hematocrit, sedimentation rate, and white blood count. During fluphenazine treatment a white blood count was obtained at weekly intervals together with a sedimentation rate and hematocrit.

Results

During the course of the drug-free and placebo phases nine of the 24 patients became so regressed that they had to be placed on fluphenazine treatment. Six of the nine regressed during the drug-free period and three during the placebo period. All patients had regressed within nine weeks following the cessation of their original phenothiazine medications. An investigation of the characteristics of the regressed group compared to those who maintained a relatively stable course revealed that in terms of original total normality mean score difference the regressed group was significantly more pathological than the non-regressed group (20.78 vs. 29.20, $t=2.08$, $P<.05$). Although the regressed group was somewhat older, no statistical difference could be found between the two groups in terms of age, nor in length of hospitalization.

Table I presents the characteristics of the regressed and non-regressed groups and their mean total and interview normality scores for the various treatment phases. For both of these scores a high score is indicative of less pathology. The mean interview normality scores (based on the psychologist's interview observations) are presented since no control was exercised over the ward observers' awareness of the drug-free intervals. Such awareness could possibly contribute to whatever differential treatment effects might be found.

An analysis of variance of the total normality scores (including ward and interview observations) of the regressed group over the three categories: initial drug phase, point of regression—occurring during the drug-free or placebo phases—and fluphena-

TABLE I

Characteristics of the Regressed and Non-Regressed Groups and Their Mean MSRPP Total and Interview Normality Scores for the Various Experimental Stages*

Group	Mean Age	Mean Length of Hosp. (Years)	Initial Degree of Normality (Total Normality Mean)	Mean Total and Interview Normality at End of Each Treatment Phase and at Point of Regression					
					Original Drug		Drug Free	Placebo	Regression	Fluphenazine
Regressed (N = 9)	42	13.3	20.78	(Total)	25.89	——	——	16.67	27.00
				(Interview)	17.56	——	——	12.00	19.33
Non-regressed (N = 15)	38	13.7	29.20	(Total)	30.13	30.13	27.73	——	28.87
				(Interview)	18.53	20.07	18.40	——	19.60

*Higher scores are indicative of less pathology. The highest possible total normality score (ward plus interview) is 62; the highest interview score is 40.

zine phase, revealed an F ratio of 8.09, which is significant at the .01 level (2 and 16 df.). The *t* ratios performed between successive mean ratings revealed that there was no significant difference between the mean total normality score of the initial drug phase and the mean score at the point of regression, although the difference in means is in the expected direction. The *t* ratio between the mean normality score at the point of regression and the mean score after fluphenazine treatment was found to be 4.89, which is significant at the .01 level.

An analysis of variance was then performed using the psychologist's interview normality score only since the ward observers were necessarily aware of medication the patients were receiving. Also, their observations entered into decisions as to the extent of regression and hence into changes in drug schedules. The interviewing psychologist, on the other hand, was totally unaware of the medication schedule, i.e., active drug, drug-free, or placebo and was also unaware of the clinical judgments involved in changes in schedules. The findings of this analysis are in essential agreement with the above. The resulting F ratio of 5.72 is significant at the .05 level; the *t* ratio between initial drug and regression means is not significant; while that between regression and fluphenazine is significant at the .01 level ($t = 3.72$).

For the non-regressed group no significant differential treatment effects over the four treatment phases (initial drug, drug-free, placebo and fluphenazine) could be found by means of analysis of variance. This finding is in agreement with the clinical observations of the research psychiatrist, in whose judgment these patients had maintained a relatively unchanged clinical course.

In the 28 patients who were followed clinically through all phases of the study, including 26 patients on whom psychological evaluations were possible (24 of these patients completed the project) and two patients who could not be evaluated in terms of the measuring instruments, but who, nevertheless, also completed the project, the following complications were observed during fluphenazine treatment: *extrapyramidal reactions*—five patients (the addition of cogentin allowed the completion of treatment for these patients); *leukopenia*—one patient (the WBC fell below 4000 after several weeks of treatment and medication was discontinued); and *sore throat and fever*—one patient (this complication developed after four weeks of treatment and medication was immediately discontinued).

Discussion

The experiences with fluphenazine reported above tend to confirm the observations of past investigators that in terms of dosage, the drug is an exceptionally potent one. The average dosage for hospitalized psychiatric patients appears to be half that reported for trifluoperazine. The range between therapeutic effect and the onset of extrapyramidal symptoms seems to be a narrow one. At the present time the advantages and disadvantages of such a narrow range with a drug of

this type versus the wide range of a drug such as chlorpromazine can only be hypothetical in nature but will become more apparent as the use of the drug is continued.

An apparent advantage of fluphenazine is that it can be administered on a once or twice daily basis, which makes its administration less time consuming. Where there are large patient populations receiving medication such a seemingly trivial factor can, in reality, bring about a decided saving in nursing time. On the other hand, careful attention is required to see that the medication is actually taken.

The patients in the present study who became hyperactive, agitated, and increasingly aggressive when their phenothiazine medications were discontinued, responded exceptionally well to fluphenazine. However, there was no evidence to indicate that their response to fluphenazine brought about a higher level of integration than had already been achieved by former medication. Those patients who displayed no change in their clinical status during the drug-free and placebo phases of the study tended to show no improvement when placed on fluphenazine. It is of interest to note here that approximately one-third of the patients in the study (9 out of 28) showed regressive behavior within a nine week period following the cessation of original phenothiazine medication.

The attrition rate of this study was relatively high, due in part to a policy of subordinating administrative control of patients to the medical realities of the hospital situation. If anything, the selective factors operating in the loss of subjects were those that would be expected to act as suppressors on measures of positive drug reactivity inasmuch as remainders tended to be somewhat older than the original group selected (40 years vs. 38 years), slightly less "normal" (26 vs. 28), and somewhat longer hospitalized (13.5 years vs. 10.3 years).

The results of the present study have raised several investigative issues regarding the factors leading to a heightened state of irritability and hyperactivity resulting in one group of patients and not in another when tranquilizer medication is discontinued. Apparently one factor is severity of illness in terms of symptom manifestation. But are there metabolic or psychodynamic differences between such patients and if so, how can they best be measured? Also, will the pattern of reactivity in those patients who become disturbed be repeated in a fairly constant manner provided environmental factors remain the same? It is our opinion that it will not since we suspect that the factors which influence the pattern of regressive behavior vary in the same individual from time to time.

Conclusion

In the treatment of the hyperactive, irritable, disturbed psychiatric patient fluphenazine demonstrated a unique potency in terms of dosage, as indicated by a dosage range of 1-5 mg., administered on a q.d. or b.i.d. basis, which generally brought about a marked improvement in this type of patient. In the non-reactive psychiatric patient the drug did not appear to bring about additional improvement. Complications occurring which could be directly traced to drug intake were extrapyramidal symptoms and leukopenia.

Acknowledgments: The authors wish to thank Mr. J. Kenneth McCusker for his psychological evaluations in this study. Appreciation is also expressed to the Squibb Institute for Medical Research for providing supplies of Prolixin (fluphenazine) and funds to carry out this research project, and to Dr. Isadore Tuerk, Superintendent, and Dr. Bruno Radauskas, Clinical Director of the Spring Grove State Hospital, for making patients and hospital facilities available. The project was administered by Friends of Psychiatric Research, Inc., Baltimore, Md.

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A Comparative Study of Two Methods of Insulin Coma Therapy

OSCAR ROZETT, M.D., and PAUL SINGER, M.D.

The purpose of this paper is to compare a conventional single dose injection method of induction of insulin coma with the multiple dose method of H. Peter Laqueur and Harry A. LaBurt. As a form of introduction it perhaps should be emphasized that we are neither proponents nor opponents of either pharmacotherapy or insulin therapy. We maintain a 17 bed insulin unit in a small hospital with a total capacity of 85 beds. We have always believed insulin therapy was the treatment of choice for most types of schizophrenia and our experiences with the newer pharmacotherapeutic agents have not altered our opinions. We use drug therapy; we believe it has its indications. We have seen good results with drugs in numerous instances where the physical forms of treatment failed. To completely disallow the newer drugs is without doubt a refusal to move forward, but to discontinue the use of insulin therapy and electroshock therapy as has been done in many hospitals is, in our opinion, a definite backward step. We utilize combined insulin and ECT wherever indicated and in many instances we combine insulin therapy with one of the tranquilizers if we feel there is an indication for it and if we feel that the patient will benefit. Our faith in insulin is continually being sustained, not only by our gratifying results, but also by the numerous psychiatrists who refer patients to us specifically for insulin shock therapy. Most of these patients have been failures on ECT and/or pharmacotherapy before coming to our hospital.

Laqueur and LaBurt who performed their work at Creedmoor State Hospital in Queens Village, New York, postulated numerous advantages to the multiple dose method. They stated that there had been no fatalities or irreversible comas and only one prolonged coma. They found a reduction in secondary hypoglycemic reactions in the afternoon and evening, and they also considered the patient less anxious, excited and restless. They found lesser gain in weight than by the single dose method and consequent saving in the amount of insulin necessary, in the amount of glucose and sugar used, as well as in the number of attendants required during therapy. We compared a series of 115 cases treated with the single dose method with 100 cases treated with the multiple dose method. The cases were consecutively taken between the years 1955 to 1960 and the patients fell essentially into the same diagnostic categories. Dietary conditions were the same for both groups of patients. The cases for insulin therapy were grouped as follows:

Schizophrenia, simple type	2
Schizophrenia, chronic undifferentiated type	27
Schizophrenia, acute undifferentiated type	3
Schizophrenia, catatonic type	7
Schizophrenia, hebephrenic type	1
Schizophrenia, paranoid type	36
Schizophrenia, chronic residual type	4
Schizophrenia, schizo-affective type	3
Schizophrenia, childhood type	1
Manic depressive, depressed type	15
Manic depressive, manic type	2
Manic depressive, mixed type	1
Paranoid state	2
Involutional psychotic reaction	2
Schizoid personality with anxiety reaction	3
Psychoneurosis, phobic reaction	2
Psychoneurosis, obsessive compulsive reaction	4
Total	115

We endeavored in all instances to administer 40 or more comas, as we feel that the results are more lasting. This however could not be achieved in all instances, as treatments had to be discontinued for various reasons which have no bearing on the results. Of the 115 patients treated with the single dose method, 8 received 50 insulin injections or more; 16 patients had between 40 and 50 injections; 37 received between 30 and 40; 33 between 20 and 30, and 21 had less than

From Fair Oaks Hospital, Summit, N. J.

20 injections. We attempted to reach 3rd stage comas as is described in numerous texts. All of the patients were discharged and the results obtained indicated that 102 patients were improved at the time of discharge, 10 were slightly improved and 3 were unimproved. Figures concerning rehospitalization since 1956 were significant. Of the 46 patients receiving 20 or more 3rd stage comas, a little less than 29% were readmitted. Of the 53 patients receiving less than 20 comas, more than 50% required readmission.

The multiple dose technique was employed in the treatment of 100 consecutive patients who, as was pointed out earlier, fell essentially into the same diagnostic categories as the control series. This was not necessarily due to our attempt at selection of cases, but simply to the fact that the breakdown of our admissions year after year over the past 10 years has been essentially the same. There were no fatalities or prolonged comas in either series.

Our first objective was to compare the average amount of insulin required to achieve deep coma. We needed somewhat less in the multiple dose method but we do not believe the difference was significant. The average dose required was 300.5 units of insulin with the multiple dose method as compared to 309.6 units with the single dose.

Our next point of comparison was the number of injections required to get a patient into 3rd stage coma. In all instances, the daily dosage was increased by a total of 30 units daily. We found that with the single dose method, 10⅓ injections were required to achieve deep coma, whereas 10 injections were required with the multiple dose method.

We then studied the undesirable side reactions that we encountered in the two series, and found that slightly protracted comas had occurred in 20 instances with the single dose method and in 15 instances with the multiple dose method. In both types of treatments, laryngeal spasms were observed on three occasions. There were 44 (38%) grand mal convulsions with the single dose method in 115 cases and 55 (55%) grand mal convulsions in 100 cases treated with the multiple dose method. In the single dose method we had 215 late afternoon insulin reactions as compared to 161 with the multiple dose method. Termination of these reactions were accomplished by oral feeding in 168 out of 215 in the single dose group and in 138 instances out of 161 in the multiple dose group. Intravenous termination of the secondary reactions was required in 47 instances as compared to 23 instances in comparing the single dose with the multiple dose method. We did find that patients with the split dose method were somewhat less anxious, restless and drowsy during the first two hours of treatment but from there on in until termination, their condition appeared to be the same with both methods. On the other hand, those patients receiving single injections appear less apprehensive at the time of the first injection. They seem to fall asleep more easily and readily when they know they are not going to receive any more injections of insulin.

It so happens, four patients were treated by both methods and in comparing their weight gain week by week, our findings were exactly opposite those reported by Laqueur and LaBurt.

As a conclusion, we feel that we have proved to our satisfaction that although the multiple dose method of Laqueur and LaBurt has merit, it does not show sufficient advantage to warrant administering three injections at 15 minute intervals, as against the simpler and less painful method of one injection of insulin a day per patient. We have terminated our study and have returned to our former single dose method, which we will continue to use until further studies will warrant our reevaluating the situation.

Effects of a New Tranquilizer, Valmethamide, in Psychiatric Outpatient Care

MARTIN GOLDBERG, M.D.

This is a preliminary investigation assessing the possible effects of a new drug in the management of patients with disturbing psychological symptoms. Valmethamide is a simple alipatic amide (2-ethyl-3-methylvaleramide) with this chemical formula:

$$CH_3CH_2(CH_3)CH\ (C_2H_5)CONH_2$$

In pharmacological studies, the response in animals indicated that this compound is capable of producing a mild effect such as detached serenity. Because of this and because valmethamide has a chemical structure considerably different from any currently available tranquilizer, this study was undertaken.

The group of subjects studied were patients seen in a private psychiatry office practice on an outpatient basis. The patients were chosen at random without regard to clinical diagnosis and with the single criterion that symptomatic distress (severe anxiety, depression, psychosomatic symptoms, etc.) was interfering with their everyday functioning and/or ability to work.

All of the patients were undergoing psychotherapy in which an effort was being made to discover the causes of the underlying emotional conflicts responsible for producing their disorder and symptoms and to increase the patient's awareness. In the course of such psychotherapy, it is often necessary to utilize medication to alleviate the patient's symptomatic distress so that he is able to continue to function in his life situation and can be accessible to the interchange of communication involved in the psychotherapeutic process.

The valmethamide used in these studies was supplied by McNeil Laboratories, Philadelphia, Pennsylvania, under the code designation of McN-X181 It will be commercially available under the trade name Axiquel.

From Institute of the Pennsylvania Hospital, Philadelphia, Pennsylvania.

Procedure

Valmethamide was evaluated over a period of 20 months as an adjunct to the psychotherapy of 35 patients, 12 men and 23 women, ranging in age from 19 to 68 years. The drug was dispensed in 200 mg. tablets for oral ingestion. The dosage was either 200 mg. or 400 mg., generally on a three- or four-times-a-day schedule. In a number of cases, however, the medication was taken only on a "p.r.n." (as necessary) basis, either at the therapist's instruction or at the patient's request. These patients usually took the tablets once or twice a day at times of unusual stress. When patients were first given the drug they were told simply that this was a new drug that might be helpful in alleviating their symptoms. Duration of treatment ranged from one week, in acute situations, to 15 months, with continuing psychotherapy, and averaged about eight weeks.

Results

Results obtained from the medication were assessed on the basis of the patient's report of his ability to function at his work, plus the psychiatrist's direct observation of symptomatology exhibited and patient's ability to function in the therapy hours. Since all these patients were in psychotherapy they were seen frequently and at considerable length by the psychiatrist. Virtually each was seen at least once weekly from 30 minutes to one hour, and many were seen as often as two to five times weekly.

Results of the administration of valmethamide are summarized in Table I. The rating categories used in this chart were defined as follows:

"Good Improvement" indicates that troublesome symptoms either completely disappeared or were so ameliorated that they no longer interfered with functions of daily living.

"Some Improvement" denotes that the symptoms

were diminished in amount and intensity but were still annoying to the patient and/or were interfering with his functioning.

"No Improvement" and "Worse" are self-explanatory.

TABLE I

Results of Treatment

Diagnosis	No. Pts.	Improvement: Good	Some	None	Worse
Anxiety Reaction	15	14	1	–	–
Schizophrenic Reaction with Anxiety	3	2	–	1	–
Agitated Depressive Reaction	8	5	2	1	–
Psychosomatic Reaction	4	1	–	3	–
Postconcussion Syndrome	3	1	1	1	–
Manic - Depressive Reaction, Manic Type	2	2	–	–	–
Totals	35	25	4	6	0

The results summarized in Table I indicate that valmethamide was effective in controlling anxiety in neurotic patients and agitation in depressed patients. It was ineffective in controlling the various disturbing symptoms encountered in psychosomatic reactions, such as pains, bodily tension, etc. There were too few psychotic patients in this group to give any indication of the drug's effect on such reaction.

Of the five patients with agitated depressive reactions who showed good symptomatic improvement, four were given concurrent treatment with antidepressants. In these patients, the valmethamide was given in an attempt to control the agitation, which was unchanged or aggravated by the antidepressants alone; and in each instance the final result was excellent control and remission of both the depression and the agitation with the combination of the two drugs.

Side Effects

Of particular interest was the paucity of side effects in the dosages used. Side effects encountered with valmethamide are summarized in Table II.

Among the 35 patients receiving the drug, only two side effects were noted: Two patients were troubled by feelings of unreality, but were able to continue with valmethamide as an adjunct to their psychotherapy. One patient developed ankle edema after taking 200 mg. of valmethamide three times a day for about 10 days. This unexplained edema cleared when the drug was stopped and there were no complications.

Of the 35 patients in this study, 26 had previously been treated with tranquilizers in an attempt to control their symptoms. Table III gives a comparison of the results in these patients, both in terms of control of symptoms and side effects while on the previous tranquilizer and on valmethamide. It would appear, in this group, that valmethamnde was about equally effective in controlling the symptoms but caused a significantly smaller number of undesired side effects.

Complete blood counts were performed on 25 patients receiving prolonged therapy and

TABLE II

Side Effects and Adverse Reactions

Side Effect or Adverse Reaction	Number Patients
Feelings of unreality	2
Ankle edema	1
Changes in blood or urine	0
Grogginess or sleepiness	0
Nausea	0
Skin reactions	0
Postural hypotension, dizziness	0
Feelings of depression, crying spells	0
Total	3

TABLE III

Comparison of Symptom Control and Side Effects with Other Tranquilizers

Previous Tranquilizer	No. of Pts.	Adequate Control of Symptoms: with Previous Drug	with Valmethamide	Troublesome Side Effects: with Previous Drug	with Valmethamide
Phenothiazines	12	9	9	6*	0
Meprobamate	12	7	9	8†	2‡
Others	2	0	2	0	0

* — Chiefly parkinsonism; also agranulocytosis, sleepiness, grogginess.

† — Chiefly sleepiness, grogginess; also depression, crying spells, impaired coordination and depth perception.

‡ — Ankle edema, feelings of unreality.

were repeated at intervals during their treatment with valmethamide. No abnormalities were reported.

Discussion

In the course of prescribing valmethamide at random for psychiatric out-patients requiring symptomatic relief, control over the following symptoms was attempted: excessive anxiety in neurotic patients; excessive anxiety in ambulatory schizophrenic patients; agitation in patients with agitated depression; pains, physical discomfort, and bodily tension in patients with psychosomatic reactions; and hyperactivity in patients with manic-depressive reactions of the manic type.

It should be noted that simple depression, in contrast to agitated depression, was arbitrarily excluded as a possible target symptom for valmethamide because the pharmacological studies indicated a possible tranquilizer-sedative action rather than any antidepressant or energizing action.

Most patients reported the impression that the medication was not long-acting and its effects seemed to "wear off" after two to four hours on an oral dose of 200 mg. Patients tended to describe their improvement in terms of "being more relaxed"; feeling a marked diminution of fears and general fearfulness, decreased feelings of tenseness, feeling less excited, jittery, jumpy, etc. Improvement was noted quickly after beginning regular dosages of valmethamide by most of the group showing good results, but an additional, cumulative improvement also occurred.

Summary

Valmethamide, a new tranquilizer, was tested over a period of 20 months in a group of 35 private out-patients undergoing psychotherapy and who required medication for control of symptoms of tension and anxiety which were disturbing their daily living pattern.

In 25 of these patients, good control of symptoms was obtained while using valmethamide in average doses of 200 to 400 mg. three or four times daily. In the other 10 patients, symptoms were either unimproved or were ameliorated but not to a degree sufficient for comfort in functioning.

Side effects with valmethamide were remarkably infrequent. No frankly sedative or depressant action or impairment of coordination was observed in the dosages used. One patient in the group studied developed ankle edema while on valmethamide and further study of this effect will certainly be required.

When the group of patients in whom good results were obtained and the group in which results were considered a failure are broken down into diagnostic categories, the results suggest that valmethamide may be highly effective in controlling anxiety in neurotic reactions and the agitation accompanying many depressions.

Book Reviews

PARKINSONISM, ITS MEDICAL AND SURGICAL THERAPY. Irving S. Cooper, M.D. Pp. 239. Charles S. Thomas, Springfield, Illinois, 1961.

The pathological physiology and the treatment of the Parkinson syndrome and related involuntary movement disorders is the central subject matter of this monograph reporting the investigation, initiated in 1952, of 5,000 patients with parkinsonism, 1,500 of whom were selected for basal ganglion operations. The problem is fully outlined from the viewpoints of medical and surgical therapy, psychotherapy, and physical therapy and rehabilitation. There is a review of surgical approaches beginning with the pyramidal era, through sympathectomy, to the present basal ganglia operations extending from the radicular to the cortical level. Factual data are presented on criteria for selection of patients, techniques, results of neurosurgical intervention, and complications. Anterior choroidal artery occlusion, chemopallidectomy, and chemothalmectomy are fully described and analyzed. Roentgeno-anatomico-clinical correlations are summarized, and fifty complete case histories are presented and illustrated.

The author has been eminently successful in fulfilling his stated purpose of describing the therapy of parkinsonism comprehensively, and of summarizing this investigation of the neurosurgical alleviation of the disease. The text is considerably enriched by the multidisciplinary approach involving

neurosurgery, internal medicine, neurology, psychology, rehabilitation, orthopedics, electrophysiology, neuroanatomy, neuropathology, and biochemistry. The medical art and photography contribute notably toward clarifying and illustrating the material. This book cannot fail to be of interest and value in the many fields involved in work with this disorder.

F. J. Braceland, M.D.

THE SPINAL CORD, BASIC ASPECTS AND SURGICAL CONSIDERATIONS. George Austin, pp. 532. Charles C. Thomas, Springfield, Illinois, 1961.

George Austin has here compiled an authoritative volume of material on the spinal cord, covering associated problems in physiology, pathology, anatomy, and related clinical specialties. Collaboration in this massive project was provided by Dr. John J. Murphy, William W. Chambers, Ph.D., Chan-Nao Liu, Ph.D., Dr. E. Horne Craigie, Dr. William James Erdman, II, Dr. Eleanor M. Bendler, Dr. Grayson McCough, Dr. Jeff Minckler, Dr. Vincent Hinck, and Dr. John Roth. All sections are documented with ample case histories; illustrations and line drawings supplement the text; a mass of carefully compiled statistics accompanies many chapters. An outstanding list of 702 references indicates the vast amount of study and research involved in this work. Both subjects and name indices are most complete.

Spinal trauma is covered from classification to treatment. Illustrations and analytic statistics in the chapter on tumors of the spinal cord are particularly striking. There is a section on the diagnosis and treatment of intervertebral disc disease. The basic aspects of anatomy, vascular supply, and physiology are individually treated. The section on neuroroentgenology is amply illustrated with plates and diagrams. The urological aspects of surgery of the spinal cord are discussed from the standpoint of neuroanatomy and neurophysiology of the genitourinary system, as well as from the point of view of diagnosis and treatment. Histologic elements and their reactions are considered under pathology. There is a section on rehabilitation of patients with spinal cord disease. The text concludes with two chapters by Dr. Austin on Regeneration of the Spinal Cord, and on Dermatomes, Sclerotomes and Spinal Cord Relationships.

The excellent quality of the text, together with the masterful art work, comprehensive coverage, and fine organization, combine to produce a well rounded work of major interest to research workers and clinicians.

F. J. Braceland, M.D.

DEPRESSION: MOOD, SYMPTOM, SYNDROME. R. A. Cleghorn, M.D., and G. C. Surtis, M.D. Documenta Geigy; Acta Psychosomatica, No. 2, J. R. Geigy, Switzerland.

This monograph is geared to provide the nonpsychiatrist as well as the psychiatrist with basic information. In the historical introduction, melancholia is traced back to the black bile and phlegm of Hippocrates. The contributions of Aretaeus, Galen, Mercurialis, Boerhaave, Pinel, Esquirol, Falret, Kraepelin and others are mentioned. In "Concepts of Depression," the differences between normal mood changes and pathological states are emphasized.

In "Clinical Aspects," the varying pictures are presented. The four cardinal vegetative signs are noted to be: 1) insomnia, especially early waking; 2) anorexia and weight loss; 3) constipation; and 4) reduced or absent menstruation in women and loss of desire and impotence in men.

In their discussion of somatopsychic depression, the authors point up that it may be pharmacological (reserpine and adrenal steroids); post-infective, metabolic (Addison's Disease); pre-menstrual or post-partum. Considerations of the etiology stress the interplay of somatic and psychological factors.

This monograph, a worthy successor to Acta Psychosomatica #1, is a most worthwhile contribution. One can only wait and hope that future monographs will cover other aspects of this prevalent and most painful illness.

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